Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende dupilumab til behandling af svær astma

Vers. 1.0

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. dupilumab
2. Ansøgers endelige ansøgning vedr. dupilumab

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Forhandlingsnotat

30.09.2022

DBS/ECH

Dato for behandling i Medicinrådet	26.10.2022
Leverandør	Sanofi
Lægemiddel	Dupixent (Dupilumab)
Ansøgt indikation	Tillæg til vedligeholdelsesbehandling til børn i alderen 6-11 år med svær astma med type 2-inflammation karakteriseret ved forhøjet eosinofiltal i blodet og/eller forhøjet fraktion af ekshaleret nitrogenoxid (FeNO), der ikke er tilstrækkeligt kontrolleret med højdosis inhalationskortikosteroid (ICS) plus et andet lægemiddel til vedligeholdelsesbehandling.

Forhandlingsresultat

Amgros har følgende pris på Dupixent (dupilumab):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke/form	Pakningsstr.	AIP (DKK)	Nuværende SAIP (DKK)	NY SAIP Pr. 1.11.22	Rabat ift. AIP
Dupixent (dupilumab)	200 mg/SC	2 stk.	8.404,83	[redacted]	[redacted]	[redacted]
Dupixent (dupilumab)	300 mg/SC	2 stk.	8.899,90	[redacted]	[redacted]	[redacted]

Dupixent (dupilumab) indgik i det udbud, som blev gennemført på baggrund af behandlingsvejledningen for svær astma. Nuværende aftale løber indtil 31.03.2023.

Prisen er gældende fra den 1.11.2022, når prisreguleringen er gennemført for terapiområdet svær astma grundet indikationsudvidelse til svær kronisk rhinosinuitis med næsepolypper (CRSwNP).

Konkurrencesituationen

Indtil nu har det kun været Xolair (omalizumab) som er godkendt til behandling af børn i alderen 6-11 år med svær astma.

Tabel 2: Sammenligning af lægemiddelpriser

Lægemiddel	Dosis	Pakningspris SAIP	Antal pakninger/år	Årlig lægemiddelpris SAIP pr. år
Dupixent (dupilumab)	300 mg hver 4. uge*	[redacted]	6,5	[redacted]
Xolair (omalizumab) 75 mg	300 mg hver 4. uge	[redacted]	52	[redacted]
	450 mg hver 4.uge	[redacted]	78	[redacted]
	600 mg hver 4.uge	[redacted]	104	[redacted]
Xolair (omalizumab) 150 mg	300 mg hver 4. uge	[redacted]	26	[redacted]
	450 mg hver 4.uge	[redacted]	39	[redacted]
	600 mg hver 4.uge	[redacted]	52	[redacted]

*For patienter der vejer mellem 15-60 kg.

Status fra andre lande

Norge: Anbefalet som tillægsbehandling [1]
Sverige: Ikke ansøgt til denne indikation [2]

Konklusion

Det er Amgros' vurdering af vi har fået den bedst mulige pris. Dette er en mindre patient population og med denne pris er behandlingen konkurrencedygtigt overfor Xolair.

[1] Dupilumab (Dupixent) - Indikasjon VI (nyemetoder.no)
[2] Beslutsunderlag Dupixent (tlv.se)

Application for the assessment of Dupixent® as add-on maintenance treatment for severe allergic asthma or severe eosinophilic asthma in children aged 6-11 years

Table of contents

N is used to calculate alpha & beta for all parameters that use a beta distribution. N should not be interpreted as a standard error

[redacted]

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1. Basic information

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Overview of the pharmaceutical	
Proprietary name	Dupixent
Generic name	Dupilumab
Marketing authorization holder in Denmark	Sanofi A/S
ATC code	D11AH05
Pharmacotherapeutic group	Other dermatological preparations, agents for dermatitis, excluding corticosteroids

Overview of the pharmaceutical	
Active substance(s)	Dupilumab
Pharmaceutical form(s)	200 mg or 300 mg solution for injection
Mechanism of action	It is a fully human monoclonal antibody against interleukin (IL)-4 receptor alpha that inhibits IL-4/IL-13 signaling
Dosage regimen	The recommended dosing of dupilumab for paediatric patients aged 6 to 11 years is according to body weight, as illustrated below: **Body weight** / **Initial and subsequent dosing** 15 to less than 30 kg: 300 mg every four weeks (Q4W) 30 kg to less than 60 kg: 300 mg every four weeks (Q4W) 60 kg or more: 200 mg every other week (Q2W)
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Dupilumab is indicated in children 6 to 11 years old as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO), who are inadequately controlled with medium to high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.
Other approved therapeutic indications	**Atopic Dermatitis** Moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy Severe atopic dermatitis in children 6 to 11 years old who are candidates for systemic therapy **Asthma** Adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO), who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment **Chronic rhinosinusitis with nasal polyposis (CRSwNP)** Indicated as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.
Will dispensing be restricted to hospitals?	No
Combination therapy and/or co-medication	Medium to high dose ICS plus another medicinal product for maintenance treatment.

Overview of the pharmaceutical	
Packaging – types, sizes/number of units, and concentrations	Dupilumab 200 mg or 300 mg solution for injection in pre-filled syringe: Pack size: • 2 pre-filled syringes
Orphan drug designation	No

2. Abbreviations

Abbreviation	Definition
ACQ-5	Asthma Control Questionnaire 5-item
ACQ-7	Asthma Control Questionnaire 7-item
AE	Adverse events
AESI	Adverse events of special interest
AST	American Thoracic Society
AUC	Area under the curve
C-ACT	Childhood Asthma Control Test
CEAC	Cost-effectiveness acceptability curve
DMC	Danish Medicines Council
DSA	Deterministic sensitivity analysis
EOS	Eosinophils
ER	Emergency room
ERS	European Respiratory Society
FeNO	Fractional exhaled nitric oxide
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma

GINA	Global Initiative for Asthma
GP	General practitioner
HCC	Half-cycle correction
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
ICS	Inhaled corticosteroids
IgE	Immunoglobulin E
IgG4	Immunoglobulin G4
IL-4Rα	Interleukin-4 receptor alpha
IRR	Incidence rate ratio
ITC	Indirect treatment comparison
KOL	Key Opinion Lead
LABA	Long-acting beta-2-agonist
LOAC	Loss of asthma control
LSmean	Least-squared mean
LTRA	Leukotriene receptor antagonists
LY	Life years

MCID	Minimal clinical important difference
MDI	Metered-dose inhaler
mm3	Cubic millimeter
NICE	National Institute for Health Care Excellence
NIH	National institute of Health
NRAD	National Review of Asthma Deaths
OCS	Oral corticosteroids
PAQLQ	Pediatric Asthma Quality of Life Questionnaire
PD	Pharmacodynamic
PH	Pharmacokinetic
Ppb	Parts per billion
ppFEV1	Predicted prebronchodilator forced expiratory volume in 1 second
PPP	Pharmacy purchase price
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRQLQ	Pediatric Rhinoconjunctivitis Quality of Life Questionnaire
PSA	Probabilistic sensitivity analysis
Q2W	Every 2 weeks
Q4W	Every 4 weeks

QALY	Quality-adjusted life years
QoL	Quality of life
RCT	Randomised controlled trials
RR	Rate Ratio
s.c.	Subcutaneous
SCS	Systemic corticosteroids
SABA	Short-acting beta-agonist
SAE	Serious adverse events
SLR	Systematic literature review
TEAE	Treatment emergent adverse events

3. Tables and Figures

3.1 List of Tables

3.2 List of Figures

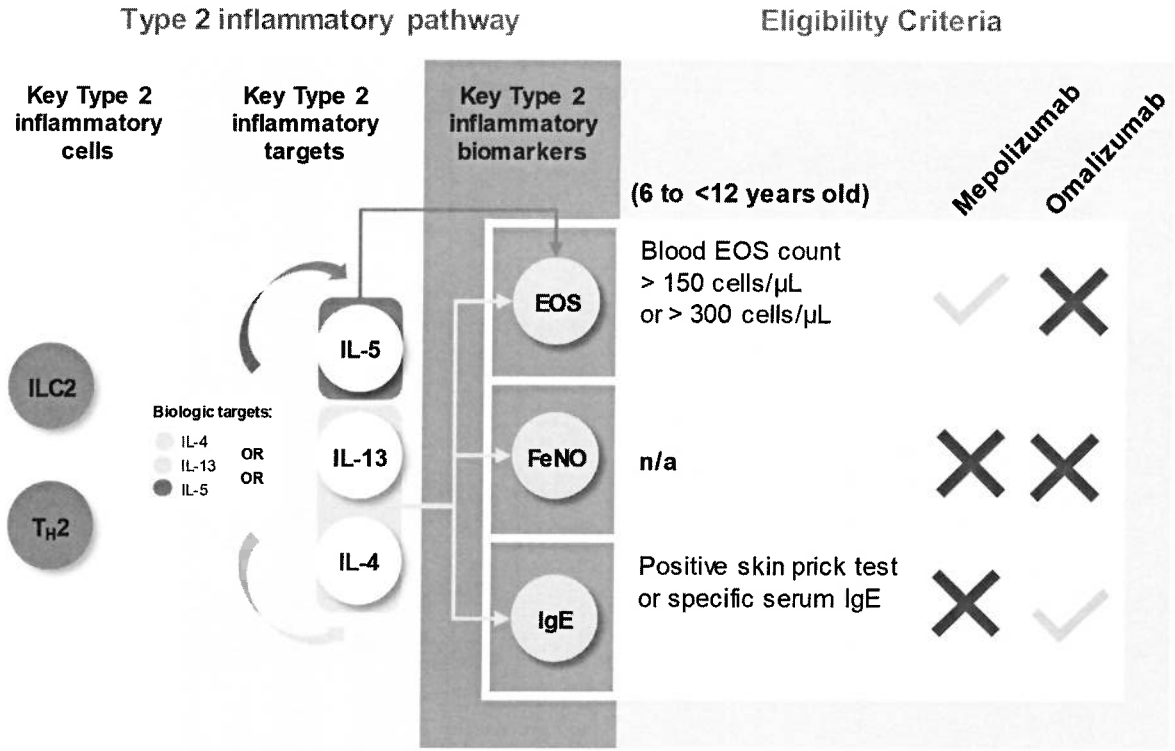
4. Summary

This single technology assessment concerns dupilumab for children with severe asthma. The active pharmaceutical ingredient of Dupixent is dupilumab and is a recombinant human monoclonal antibody of the immunoglobulin G4 (IgG4) directed against the interleukin-4 receptor alpha (IL-4Rα) subunit and thereby inhibits both IL-4 and IL-13-mediated signaling. Dupilumab is indicated in adults, adolescents and children of 6 years and above as add-on maintenance treatment for severe asthma with type 2 inflammation characterized by raised blood eosinophils (EOS) and/or raised fractional exhaled nitric oxide (FeNO), who are inadequately controlled with high-dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

Biologics currently available to treat children with asthma have limited evidence and limited efficacy, and up to half of treated children remain sub-optimally controlled, continuing to experience exacerbations (1-7). Dupilumab is the only currently available biologic that has shown improvement in lung function, which current biologics have failed to demonstrate.

Biologics currently approved for children 6 to <12 years old target a single component (IL-5 or IgE) of type 2 inflammation, and are therefore, indicated on a single biomarker criterion in the target population (8, 9). The single biomarker-based eligibility criteria limit some children with severe uncontrolled asthma from gaining control of their asthma (Figure 1) (6, 10, 11). Due to the heterogeneity of children with moderate to severe uncontrolled asthma, therapies with a novel mechanism of action that inhibits multiple type 2 inflammation pathways, such as dupilumab are needed (6, 8-11).

Figure 1. Eligibility criteria for current biologics based on the type 2 inflammatory pathway (12, 13)



EOS = eosinophil; FeNO = fractional exhaled nitric oxide; IgE = immunoglobulin E; IL = interleukin; ILC2 = Type 2 innate lymphoid cells; Th2 = T helper 2
Cytokine graphic adapted from Spahn et al. 2016 (12) and Gandhi et al. 2016 (13).

4.1 Population

Based on dialogue with the experts and feedback from DMC dialog meeting, the application will include three subpopulations, specifically:

- **Severe allergic IgE asthma,** patients aged 6 - < 12 years of age with severe asthma with type 2 inflammation characterized by allergy and concomitant eosinophilia or characterized by allergy and concomitant elevated FeNO (EOS≥150 cells/µl or FeNO≥20 ppb, total IgE ≥30 IU/mL and 20≤weight≤150 kg (IgE, body weight))
- **Severe eosinophilic asthma,** patients aged 6 - < 12 years of age with severe asthma with type 2 inflammation characterized by eosinophilia (Blood eosinophils ≥150 cells/µL)
- **Severe asthma with elevated FeNO,** patients aged 6 - < 12 years of age with severe asthma with type 2 inflammation characterized by elevated FeNO (FeNO≥20ppb)

4.2 Intervention

Dupilumab is currently indicated in adults and adolescents aged 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood EOS and/or raised FeNO in patients who are inadequately controlled by high-dose ICS plus another medicinal product for maintenance treatment. Dupilumab is recommended by the DMC for the severe allergic asthma subgroup and the severe eosinophilic asthma subgroup for adults and adolescents aged 12 years and older(14).

4.3 Comparator

Choice of comparators was in line with the current Danish treatment guidelines for the indicated patient populations. According to the treatment guideline, patients with severe allergic IgE asthma would be treated with omalizumab. The treatment guidelines do not state a recommended treatment for patients with severe eosinophil asthma, however, following discussion with the secretariat and the chairman of the expert committee mepolizumab was chosen as the relevant comparator for this population. No treatment recommendation from DMC was made for patients with severe asthma with elevated FeNO (≥20 ppb).

In the different trials, patients in the patient populations received the following treatment with placebo as comparator:

- Patients with severe allergic asthma received:
  - omalizumab, weight based s.c. Q2W or Q4W (15, 16).
- Patients with severe eosinophilic asthma received:
  - mepolizumab, weight based (40 mg <40kg, 100 mg ≥40kg) s.c. every Q4W (17, 18)
- Patients with severe asthma with elevated FeNO received:
  - Placebo

The trials were similar to the Danish clinical practice, where the treatment recommendation for patients in the different patient's populations are as followed:

- Patients with severe allergic IgE asthma received:
  - omalizumab, weight based s.c. Q2W or Q4W (19).
- Patients with severe eosinophilic asthma received:
  - No recommended treatment, however, mepolizumab, 100 mg s.c. every Q4W is mentioned within the treatment guidelines (19).
- Patients with severe asthma with elevated FeNO received:
  - No treatment recommendation (placebo will be the comparator for this population)

4.4 Outcomes

The outcomes chosen for this clinical assessment was based on the outcomes presented in the Danish treatment guidelines for severe asthma(19) and for this assessment the following outcomes were included:

- Severe asthma exacerbation rate
- Proportion of patients experiencing no exacerbations

- ppFEV1% - change from baseline
- Proportion of patients with≥200mL improvement in FEV1
- Asthma Control Questionnaire (ACQ-7 IA)
- Pediatric Asthma Quality of Life Questionnaire (PAQLQ-IA)
- Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ)
- Adverse events (AE) (%)
- Adverse events leading to discontinuations (%)
- Serious adverse events (SAE) (%)

4.5 Literature search

A global systemic literature review (SLR) was used as the evidence base for this submission, and was locally adapted to fit the scope of the assessment in Denmark. This approach is deemed feasible as the global SLR was broader and will therefore have included all studies relevant for the scope of this application.

Standard methods for conducting and reporting an SLR were used per the Cochrane Handbook(20, 21) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines(22, 23) to satisfy the requirements of the National Institute for Health Care Excellence (NICE). The SLR was conducted in February 2021, and the local adaptation was conducted in January 2022.

The local adaptation was conducted to restrict the literature included in the global SLR to international studies with dupilumab, omalizumab or mepolizumab in children with severe asthma. The local adaptation only included international multicenter studies, while excluding studies with populations not reflective of the Danish patient population. The initial scope of the global SLR was broader and included more studies with populations not relevant for the single technology assessment of dupilumab in Denmark.

Based on the references included at full-text level for the global SLR, Sanofi made a local adaptation to the Danish context, and a total of 5 references from 3 studies was included for this HTA submission(15-18, 24), which include data from the Liberty Asthma VOYAGE study, where data was not published at the time of the global SLR.

4.6 Clinical comparison – severe allergic asthma

To evaluate the efficacy and safety of dupilumab versus omalizumab, three studies were considered relevant from the literature search. All studies were both double-blinded RCTs, assessing the efficacy and safety of biological treatment in patients aged 6-11, with placebo as the comparator. One study was Liberty Asthma VOYAGE (VOYAGE), which was a randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in children 6 to <12 years of age with uncontrolled persistent asthma. Two of the three studies were evaluating the efficacy and safety of omalizumab. One of the studies by Kulus et al., 2010 was a subgroup analysis of the patients, which was relevant for this applications subgroup. Kulus et al., 2010 used data from the study with the full patient population, why both studies are mentioned, but only the results from the subgroup analysis relevant for this application are reported (15, 16).

As Liberty Asthma VOYAGE had broad eligibility criteria, subgroup analysis has been conducted using data from the Liberty Asthma VOYAGE trial, defined as:

- **Allergic asthma subgroup**: This subgroup included patients with allergy, defined as baseline total IgE≥30 IU/mL and at least one perennial allergen or one seasonal allergen specific IgE value ≥0.35 UI/mL at baseline

As few endpoints were comparable in the comparison between VOYAGE and the omalizumab trial (IA05), it was not possible to conduct indirect treatment comparison (ITC) using methods such as, a Bucher's ITC or a matching adjusted indirect comparison. For this comparison, efficacy and safety was instead compared through a narrative synthesis.

Both studies indicate that dupilumab and omalizumab reduce the risk of exacerbations significantly compared to placebo, although demonstrated in different exacerbation definitions. It is therefore not possible to conclude that dupilumab is superior to omalizumab in reducing severe exacerbation in severe allergic asthma patients.

It is highly likely that dupilumab is at par with omalizumab, if not superior in terms of the patient's quality of life while on treatment based on the PAQLQ-IA global score. However, due to the differences in study design, inclusion criteria and follow-up period, this comparison should be interpreted with caution.

Overall, it was not possible to conclude whether dupilumab was a superior treatment alternative to omalizumab. Although it appears that dupilumab and omalizumab have comparable safety profiles, based on the narrative synthesis of safety outcomes.

4.7 Clinical comparison – severe eosinophilic asthma

To evaluate the efficacy and safety of dupilumab versus mepolizumab two studies were considered relevant. One study was Liberty Asthma VOYAGE (VOYAGE), which was a randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in children 6 to <12 years of age with uncontrolled persistent asthma. The trial for mepolizumab was an open-label, non-controlled repeat-dose phase 2 trial conducted in children with severe asthma with an eosinophilic phenotype.

As Liberty Asthma VOYAGE had broad eligibility criteria, subgroup analysis has been conducted using data from the Liberty Asthma VOYAGE trial, defined as:

- **Severe eosinophilic asthma**: This subgroup included patients with baseline blood EOS ≥150 cells/µL

Due to the heterogeneity between the two studies, as well as limited data for mepolizumab, a narrative comparison has been conducted on the outcomes where possible.

The mepolizumab trial did not provide any data on exacerbations, hence not making a comparison on these endpoints possible. The narrative comparison showed that dupilumab was potentially superior in lung function and asthma control endpoints. The small samples size did not constitute a strong basis for a credible conclusion. With the weak data for mepolizumab, it was not possible to come to a definitive conclusion in this comparison.

Overall, it was not possible to conclude whether dupilumab was a superior treatment alternative to mepolizumab, due to the poor data of mepolizumab in the paediatric patient population. Although it appears that dupilumab and omalizumab have comparable safety profiles, based on the narrative synthesis of safety outcomes.

4.8 Clinical comparison – severe asthma with elevated FeNO

Only one study was found relevant to assess the efficacy and safety of dupilumab compared to placebo in children aged 6 to <12 with severe asthma with elevated FeNO, as a randomized direct head-to-head study has been conducted, in the Liberty Asthma VOYAGE trial.

As Liberty Asthma VOYAGE had broad eligibility criteria, subgroup analysis has been conducted using data from the Liberty Asthma VOYAGE trial, defined as:

- **Severe asthma with elevated FeNO**: Data is not sufficient to create a valid subgroup analysis for a subpopulation with elevated FeNO patients without concomitant eosinophilia and without concomitant allergy. Therefore, available data for patients with elevated baseline FeNO (≥20 ppb) regardless of EOS and allergy status is provided instead.

Efficacy summary

Table 1. Summary of study results Dupilumab, children with severe asthma with elevated FeNO, efficacy outcomes

Outcome	Dupilumab (n=254)	Placebo (n=130)	AD (95% CI)	RD (95% CI)	p-value
Efficacy results					
Annualized rate of severe asthma exacerbations during 52-week treatment period (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% Experience no exacerbation during 52-week treatment periods, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from BL at week 12 of ppFEV1, (±SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% patients with >=200mL improvement in FEV1 at week 12 (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from BL at week 24 of ACQ-7-IA, (±SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from BL at week 52 of PAQLQ-IA global score (+SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from BL at week 52 of PRQLQ global score (+SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD, absolute difference; BL, base line; CI, Confidence Interval; NA, not available; ppFEV1, predicted prebronchodilator FEV1; RD, relative difference. **Note**: #, p-value for RD; *, p-value for AD.

Severe exacerbations

The annualized rate of severe exacerbation events during the 52-week treatment period was [redacted] in the dupilumab arm and [redacted] in the placebo arm resulting in a statistically significant relative risk reduction [redacted] in the dupilumab-arm compared to placebo (24).

[redacted]% of the patients in the dupilumab-arm did not experience a severe exacerbation during the 52-week treatment duration, while a small proportion of patients ([redacted]%) in the placebo-arm experienced no exacerbation during the same period. Resulting in a statistically significant absolute difference of [redacted]% in favour of dupilumab.

Change from baseline in ppFEV1% to week 12

In week 12, the change from baseline was estimated [redacted] for the dupilumab group and placebo group. Dupilumab showed a significant LSmean difference [redacted] compared to placebo in the Liberty Asthma VOYAGE-trial for the subgroup with severe asthma with elevated FeNO.

%-patients with >=200mL improvement in FEV1 at week 12

At week 12, a significantly higher proportion of patients in the dupilumab group had an improvement in FEV1 of 200 mL or more ([redacted] more patients) when compared to placebo.

Asthma control

The LSmean ACQ-7-AI change from baseline in week 24 showed a change in the dupilumab group [redacted] in the placebo group, and dupilumab showed a significant improvement [redacted] compared to placebo ($p<0.001$).

Quality of life (QoL)

In the PRQLQ global score, dupilumab showed a significant mean improvement over time (indicated by lower score on the PRQLQ) [redacted] at week 52 compared to placebo.

Safety

The overall incidence of adverse events during the trial period were similar between groups in the safety population, Table 8. In the dupilumab group SAEs were reported in 13 patients and 6 in the placebo group, corresponding [redacted] in the placebo group (24). The difference was not statistically significant.

Few patients discontinued treatment due to adverse events in Liberty Asthma VOYAGE. The discontinuation rate due to AE were [redacted] patients treated with dupilumab and [redacted] for the patients treated with placebo(24).

Overall conclusion

Dupilumab is a significantly better treatment option compared to placebo and provided a clinically meaningful improvement for a wide range of efficacy endpoints. Dupilumab consistently reduced exacerbations, improved lung function, improved asthma control and QoL, compared with placebo for paediatric patients with severe asthma with elevated FeNO in the Liberty Asthma VOYAGE trial. Dupilumab was well tolerated, and no differences were observed between the dupilumab and placebo group in the Liberty Asthma VOYAGE trial.

4.9 Cost-effectiveness analysis

A Markov cohort model was developed in Microsoft excel to reflect both the chronic day-to-day asthma symptoms that patients with uncontrolled persistent asthma experience, which would influence their QoL, as well as the risk these patients may also experience intermittent asthma exacerbations that can vary in severity and in some instances, lead to death. The model structure was developed based on a previous health economic model, which was accepted by NICE(25) for severe persistent asthma in adolescent and adults and suggestions by clinicians to make sure that the structure of the model was consistent with clinical practice.

The model included 3 paediatric subgroups, aligned with subgroups in the clinical assessment:

- Severe allergic asthma
- Severe eosinophilic asthma
- Severe asthma with elevated FeNO

The model was based on efficacy and safety data from the clinical trial LIBERTY VOYAGE, omalizumab (IA05)(16), and mepolizumab(18). An exploratory Bucher ITC was used to compare dupilumab versus omalizumab and dupilumab versus mepolizumab, derived from Liberty Asthma VOYAGE, IA05, and the mepolizumab study. Health state utility values was based on the Liberty trial for the child cohort and QUEST trial for the adult/adolescent cohort. The model considered drug cost, treatment administration cost, monitoring cost and patient and transportation cost.

Results

In the severe allergic asthma subgroup, dupilumab was dominant (lower cost, higher effect) when compared with omalizumab + background therapy. In the severe eosinophilic asthma subgroup, dupilumab was dominant (lower cost, higher effect) when compared with mepolizumab + background therapy. When compared to background therapy alone, dupilumab has an ICER of [redacted] per incremental QALY (higher cost, higher effect). In the severe asthma with elevated FeNO subgroup, dupilumab has an ICER of [redacted] per incremental QALY (higher cost, higher effect).

4.10 Budget impact

A budget impact model was developed to estimate the expected budget impact of recommending dupilumab as a treatment option in Denmark. The budget impact analysis has been embedded within the cost-effectiveness model. The budget impact result is representative of the populations in the cost per patient model.

In Denmark, it is estimated that approx. 101 paediatric patients with severe asthma are eligible for treatment with dupilumab as add-on to background therapy annually. For ease of calculation in the budget impact analysis, the number of patients has been rounded to **100** patients. Of the 100 patients, [redacted]

The budget impact analysis at pharmacy purchase price (PPP) prices, indicated that the estimated budget impact of recommending dupilumab as standard treatment for patients with severe allergic asthma in Denmark at PPP is approx [redacted] in year 5. In the severe eosinophilic asthma subgroup, the estimated budget impact of recommending dupilumab as standard treatment in Denmark at PPP is approx. [redacted] in year 1 and approx. [redacted] in year 5. In the subgroup of patients with severe asthma with elevated FeNO, the estimated budget impact of recommending dupilumab as standard treatment in Denmark at PPP is approx. [redacted] every year.

5. The patient population, the intervention and choice of comparator(s)

5.1 The medical condition and patient population

Asthma is a common, chronic disorder of the airways; it is characterized by recurring symptoms such as breathlessness, wheezing and coughing, and inflammation of the airways(26). Asthma can cause acute episodes of progressively worsening symptoms associated with airflow obstruction, known as exacerbations. The performance of daily activities and patients' QoL is often limited as a result.

Persistent asthma describes asthma in patients who frequently experience symptoms that affect their daily lives(27-29). Persistent inflammation has been shown to increase bronchial hyper-responsiveness to a variety of stimuli, resulting in bronchospasm(26, 27). Furthermore, airflow obstruction reversibility may be incomplete and patients are at a higher risk of airway remodelling (permanent structural changes in the airway), which leads to more severe and persistent disease(26, 30, 31). As a consequence, persistent asthma is associated with a progressive loss of lung function and responsiveness to therapy(26, 30, 31). Persistent asthma, therefore, has a large impact on patients' QoL, morbidity, and overall mortality(27, 28).

The prevalence of asthma in children has increased strikingly since the 1950s and is now the most commonly reported non-communicable disease among children world-wide(32) with global prevalence in children estimated to be 6%(33). Severe asthma in children is associated with reduced quality of life, significant impact on social activities, missed days at school, frequent visits to emergency departments and hospitalizations, and the severe long-term consequences of progressive airflow obstruction and wors-ened overall lung function during adolescence and adulthood(30).

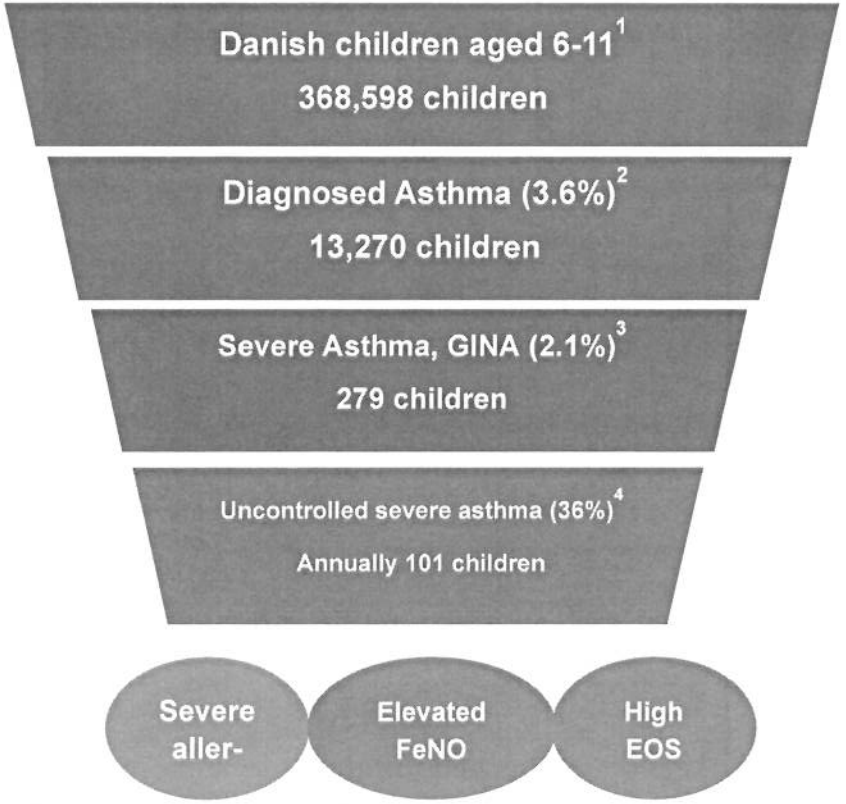
In Denmark, asthma is the most common chronic disease in children and young people and affects 10-12% of children of school age (34). Between 5 and 15% of the children have more severe asthma with bothersome, frequent day and night symptoms as well as severe exacerbations requiring medical attention and hospitalization, resulting in significant personal and socio-economic costs (35-37). Severe asthma in children is characterized by sustained symptoms despite treatment with high doses of ICS or oral corticosteroids and represents approximately 5% of childhood asthma cases (38).

The number of prevalent patients aged 6-11 years with uncontrolled severe asthma is estimated to be approx. 101 patients. This estimate is estimated using the total number of children aged 6-11 from Statistics Denmark(39), 368,598 children. 3.6% of all Danish children was diagnosed by a physician with asthma(40), resulting in approx. 13,270 children with asthma. The prevalence of severe asthma within all asthma patients is 2.1%(41), resulting in approx. 279 children with severe asthma. Of the 279 children with severe asthma, it is estimated that approx. 36% of the patients have low control of their asthma(42), resulting in approx. 101 patients with uncontrolled severe asthma. This number have been previously discussed at a dialogue meeting with the DMC. Please see the calculation in Figure 2.

Table 2. Estimated number of patients eligible for treatment with dupilumab

Year	2022	2023	2024	2025	2026
Number of patients in Denmark who are expected to be eligible for treatment with dupilumab in the coming years	101	101	101	101	101

Figure 2. Population estimates of patients aged 6–11 years with uncontrolled severe asthma



***References**: 1, Denmark Statistics, FOLK1A table, population on first day of quarter, by sex, region, time and age(43); 2, Change G, Vedsted P, Schiøtz P. Identification of asthmatic children using prescription data and diagnosis. Eur J Clin Pharmacol. 2007 Jun;63(6):605-11. doi: 10.1007/s00228-007-0286-4. Epub 2007 Mar 27. to Zilmer M, Steen NP, Zachariassen G, Duus T, Kristiansen B, Halken S. Prevalence of asthma and bronchial hyperreactivity in Danish schoolchildren: no change over 10 years. Acta Paediatr. 2011 Mar;100(3):385-9. doi: 10.1111/j.1651-2227.2010.02036.x. Epub 2010 Oct 25. 7; 3, NORDSTAR, The prevalence of severe asthma in 2018 according to ERS / ATS and GINA guidelines in four Nordic countries, Sweden, unpublished data anticipate to submit for publication Q2 2022(41); 4, von Bülow, Anna, et al. "The prevalence of severe asthma and low asthma control among Danish adults." The Journal of Allergy and Clinical Immunology: In Practice 2.6 (2014): 759-767(42).*

5.1.1 Patient populations relevant for this application

The study population of LIBERTY ASTHMA VOYAGE was children 6 to <12 years of age with a physician diagnosis of persistent asthma for ≥12 months prior to screening and uncontrolled during the screening period, based on clinical history, examination, and pulmonary function parameters according to Global Initiative for Asthma (GINA) 2015

Guidelines (44). According to the Global Initiative for Asthma (GINA) for biologic therapies targeting type 2 inflammation, GINA recommends the use of an elevated peripheral-blood eosinophil count (≥150 cells per cubic millimeter), an elevated FeNO (≥20 parts per billion [ppb]), or both as cutoff values(45).

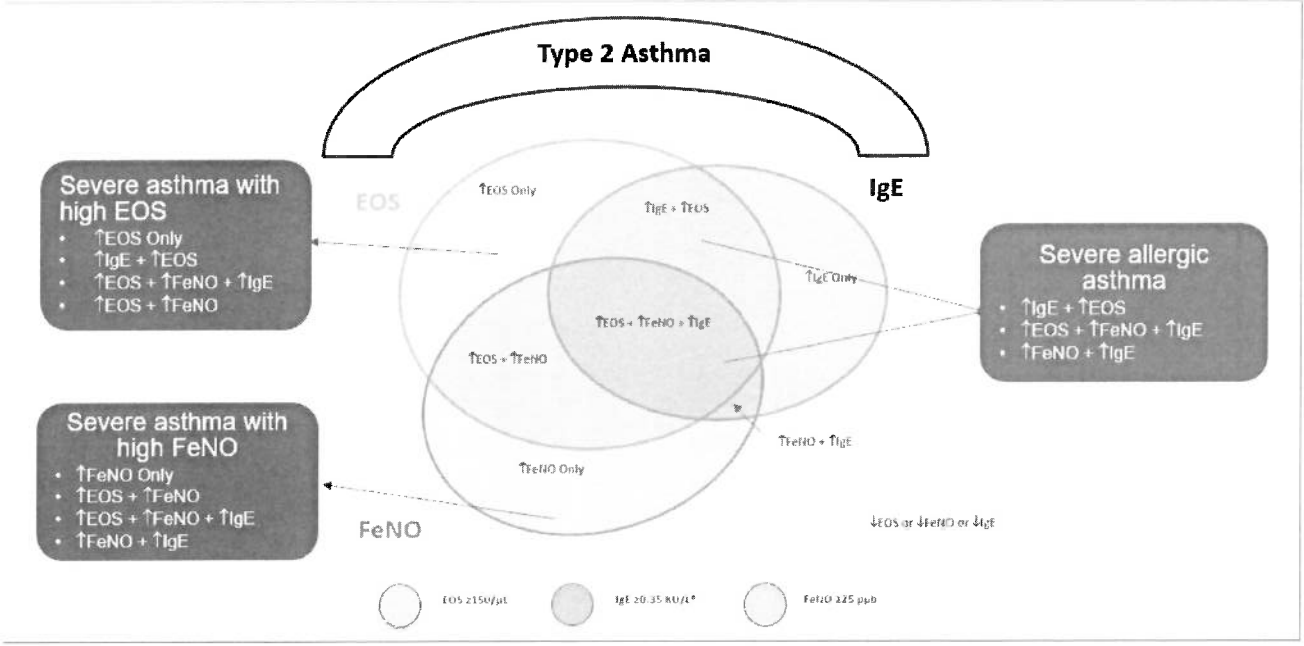
This is the same as the target population for dupilumab in the expected EMA indication.

Based on dialogue with the experts and feedback from DMC dialog meeting, the application will include three subpopulations, specifically:

- **Severe allergic IgE asthma,** patients aged 6 - < 12 years of age with severe asthma with type 2 inflammation characterized by allergy and concomitant eosinophilia or characterized by allergy and concomitant elevated FeNO (EOS≥150 cells/µl or FeNO≥20 ppb, total IgE ≥30 IU/mL and 20≤weight≤150 kg (IgE, body weight))
- **Severe eosinophilic asthma,** patients aged 6 - < 12 years of age with severe asthma with type 2 inflammation characterized by eosinophilia (Blood eosinophils ≥150 cells/µL)
- **Severe asthma with elevated FeNO,** patients aged 6 - < 12 years of age with severe asthma with type 2 inflammation characterized by elevated FeNO (FeNO≥20ppb)

These subgroups are aligned with the subgroups submitted to DMC in our application for the assessment of dupilumab as add-on maintenance treatment for severe asthma with type 2 inflammation characterized by raised blood eosinophils in adults and adolescents 12 years and older. There is a minor deviation that instead of 25 ppb for FeNO a threshold of 20 ppb was used for the VOYAGE children population.

Figure 3. Patient populations in severe asthma



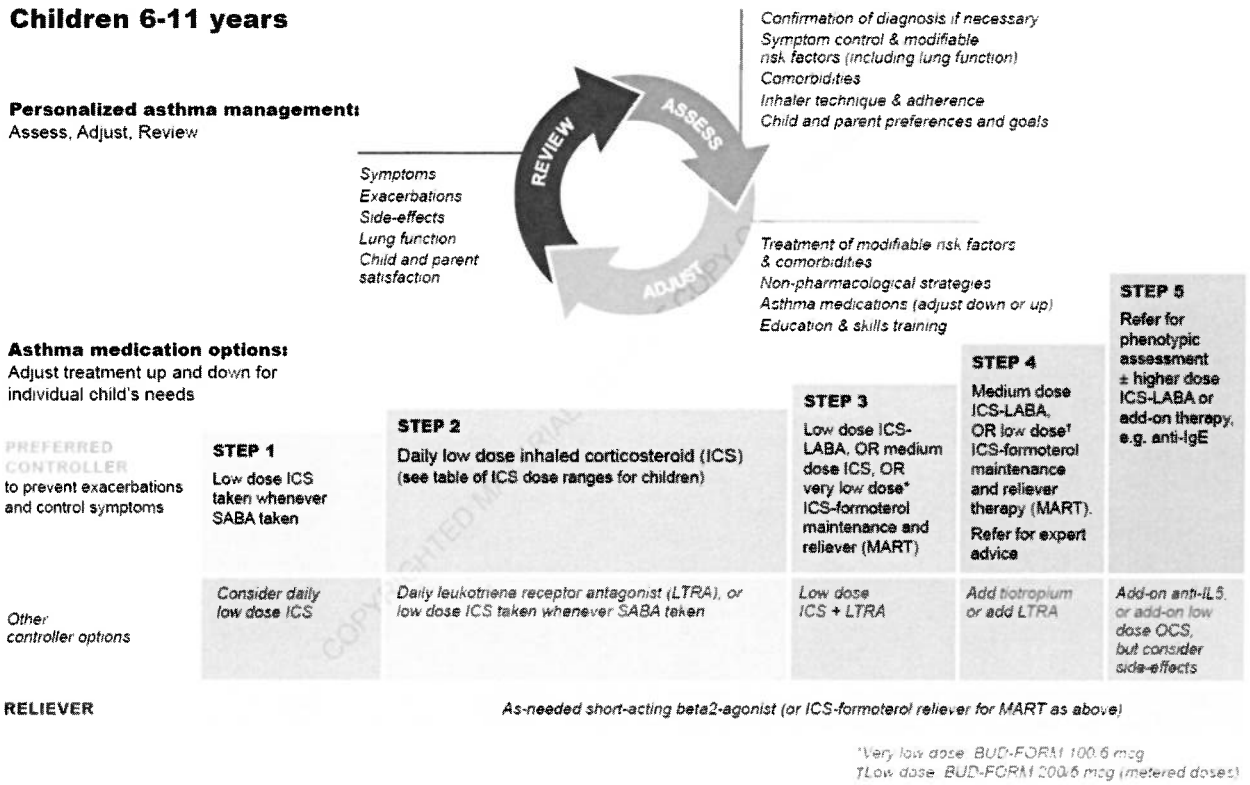
5.2 Current treatment options and choice of comparator(s)

Danish treatment practice is in line with international guidelines such as the European Respiratory Society (ERS) and American Thoracic Society (ATS) as well as the GINA guidelines (45, 46). Children aged 6-11 years with severely uncontrolled asthma are treated with medium-dose ICS combined with a long-acting beta-2-agonist (LABA) plus an as-needed short-acting beta-agonist (SABA) or low-dose ICS-formoterol maintenance and reliever (45). When adequate asthma control is not achieved, a short course of oral corticosteroids (OCS) may also be needed.

Other controller options include increasing to high paediatric dose ICS-LABA, but adverse effects must be considered (45). For example, the use of high doses of ICS and OCS is highly problematic as such therapies have the potential to affect the child's height (47). Tiotropium (a long-acting muscarinic antagonist) may be used as add-on therapy in children aged 6 and older. Leukotriene receptor antagonists (LTRA) could be considered.

Children aged 6-11 years with confirmed severe uncontrolled asthma on GINA step 4/5 treatment (see Figure 4) and with persistent symptoms despite good adherence to treatment should be referred to a specialist with expertise in the management of severe asthma (45, 46). A systematic assessment approach is recommended by Danish pulmonologists to distinguish between uncontrolled asthma and severe asthma (48). Biologics may be considered. For eosinophilic patients IL-5 inhibitors can be considered - mepolizumab is approved in Denmark for the treatment of children aged ≥6 years (34), although efficacy data for mepolizumab in children are limited to one small open-label study (17). For allergic patients, omalizumab can be considered for children aged ≥6 years with moderate or severe uncontrolled asthma (45).

Figure 4. Stepwise Approach to Asthma Treatment in Children Aged 6 to 11 as per International Guidelines (GINA 2021)(45)



Biologics are generally only indicated for patients at Step 5, as seen in Figure 4, which are severe asthma patients (49) and in Denmark there are only two biologics approved for treating severe asthma in children aged 6-11, omalizumab and mepolizumab. Omalizumab is indicated for children with severe allergic asthma, whereas mepolizumab is indicated for children with severe eosinophilic asthma (19).

5.2.1 Current treatment options

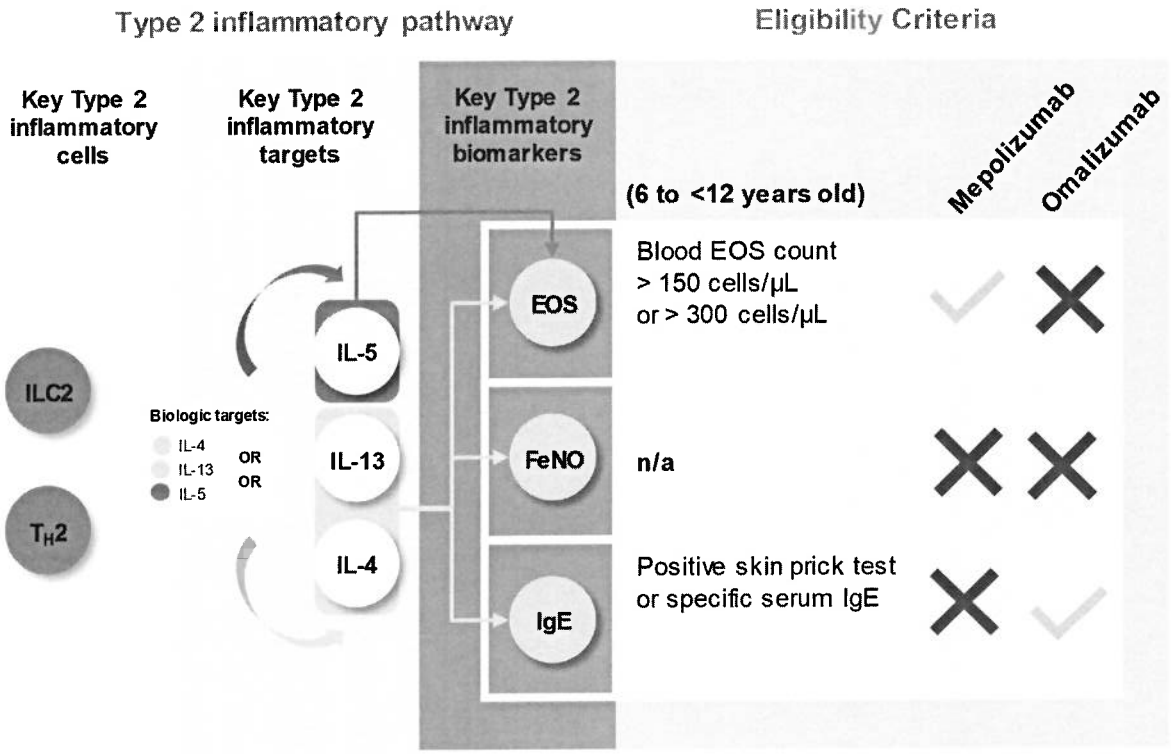
Biologics currently available to treat children with asthma have limited evidence and limited efficacy, and up to half of the treated children remain sub-optimally controlled, continuing to experience exacerbations (1-7).

Dupilumab is the only currently available biologic that has shown improvement in lung function, which current biologics have failed to demonstrate.

Biologics currently approved for children 6 to <12 years old target a single component (IL-5 or IgE) of type 2 inflammation, and are therefore, indicated on a single biomarker criterion in the target population (8, 9). The single biomarker-based eligibility criteria limit some children with severe uncontrolled asthma from gaining control of their

asthma (Figure 1) (6, 10, 11). Due to the heterogeneity of children with moderate to severe uncontrolled asthma, therapies with a novel mechanism of action that inhibits multiple type 2 inflammation pathways, such as dupilumab are needed (6, 8-11).

Figure 5. Eligibility criteria for current biologics based on the Type 2 inflammatory pathway (12, 13)



EOS = eosinophil; FeNO = fractional exhaled nitric oxide; IgE = immunoglobulin E; IL = interleukin; ILC2 = Type 2 innate lymphoid cells; Th2 = T helper 2
Cytokine graphic adapted from Spahn et al. 2016 (12) and Gandhi et al. 2016 (13).

For the indicated patient populations, the current Danish treatment guidelines states, that omalizumab is considered the standard treatment for paediatric severe allergic asthma population, whilst mepolizumab have indication for the paediatric severe eosinophilic asthma population(19, 50). There is no indicated treatment option for patients who have severe asthma with type 2 inflammation characterized by elevated FeNO without concomitant eosinophilia and without concomitant allergy.

5.2.2 Choice of comparator(s)

Choice of comparator was in line with the current Danish treatment guidelines for the indicated patient populations(50). According to the treatment guideline, patients with severe allergic asthma would be treated with omalizumab. The treatment guidelines state a recommended treatment for patients with severe eosinophil asthma, however,

following discussion with the secretariat and the chairman of the expert committee mepolizumab was chosen as the relevant comparator for this population. No treatment recommendation from DMC was made for patients with severe asthma patients with elevated FeNO.

In the different trials, patients in the patient populations revied the following treatment with placebo as comparator:

- Patients with severe allergic IgE asthma received:
  - omalizumab, weight based s.c. Q2W or Q4W (15, 16).
- Patients with severe eosinophilic asthma received:
  - mepolizumab, weight based (40 mg <40kg, 100 mg ≥40kg) s.c. every Q4W (17, 18)
- Patients with severe asthma with elevated FeNO received:
  - Placebo

The trials were similar to the Danish clinical practice, where the treatment recommendation for patients in the different patient populations are as followed:

- Patients with severe allergic IgE asthma received:
  - omalizumab, weight based s.c. Q2W or Q4W (19).
- Patients with severe eosinophilic asthma received:
  - No recommended treatment, however mepolizumab, 100 mg s.c. every Q4W is mentioned (19).
- Patients with severe asthma with elevated FeNO received:
  - No treatment recommendation (placebo will be the comparator for this population)

5.2.3 Description of the comparator(s)

Table 3. Description of omalizumab and mepolizumab

Subject	Description	
Generic name (ATC-code)	Omalizumab (R03DX05)	Mepolizumab (R03DX09)
Mode of action	Omalizumab binds to IgE and prevents binding of IgE to FcεRI (high-affinity IgE receptor) on basophils and mast cells, thereby reducing the amount of free IgE that is available to trigger the allergic cascade. Treatment with omalizumab inhibits IgE-mediated inflammation, as evidenced by reduced blood and tissue eosinophils and reduced inflammatory mediators, including IL4, IL-5, and IL-13 by innate, adaptive and non-immune cells.	Mepolizumab is a humanized monoclonal antibody (IgG1, kappa), which targets human interleukin-5 (IL-5) with high affinity and specificity. Mepolizumab inhibits the bioactivity of IL-5 with nanomolar potency by blocking the binding of IL-5 to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface, thereby inhibiting IL-5 signaling and reducing the production and survival of eosinophils

Pharmaceutical form	75mg powder and solvent for solution for injection	Powder for solution for injection
Posology	The appropriate dose and frequency of omalizumab is determined by baseline IgE (IU/ml), measured before the start of treatment, and body weight (kg). Prior to administration of the initial dose, patients should have their IgE level determined by any commercial serum total IgE assay for their dose assignment. Based on these measurements, 75 to 600 mg of omalizumab in 1 to 4 injections may be needed for each administration. The maximum recommended dose is 600 mg omalizumab every two weeks. For the dose determination charts, see Figure 21.	The recommended dose of mepolizumab is 40 mg or 100 mg administered subcutaneously once every 4 weeks.
Method of administration	Omalizumab is given as a subcutaneous injection	Mepolizumab is given as a subcutaneous injection and should be administered by a health care professional. It may be injected into the upper arm, thigh, or abdomen.
Should the pharamecutical be administered with other medicines	Omalizumab can be used with or without inhaled or oral corticosteroids.	Mepolizumab can be used with or without inhaled or oral corticosteroids.
Treatment duration / Criteria for end of treatment:	Omalizumab is intended for long-term treatment. Consider end of treatment if unacceptable toxicity, if asthma remains uncontrolled or worsens during treatment.	Mepolizumab is intended for long-term treatment. Consider end of treatment if unacceptable toxicity, if asthma remains uncontrolled or worsens during treatment.
Necessary monitoring, both during administration and during the treatment period	Clinical trials have demonstrated that it takes at least 12-16 weeks for omalizumab treatment to show effectiveness. At 16 weeks after commencing omalizumab therapy patients should be assessed by their physician for treatment effectiveness before further injections are administered. The decision to continue omalizumab following the 16-week timepoint, or on subsequent occasions, should be based on whether a marked improvement in overall asthma control is seen.	NA
Need for diagnostic or other test	Omalizumab is indicated as add-on therapy to improve asthma control in patients with severe	NA

	persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.

Abbreviations; IgE: Immunoglobulin E; FcεRI: high-affinity IgE receptor; IL: Interleukin

5.3 The intervention (dupilumab)

Dupilumab is currently indicated in adults and adolescents aged 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO in patients who are inadequately controlled by high-dose ICS plus another medicinal product for maintenance treatment. Dupilumab is recommended by the DMC for the severe allergic asthma subgroup and the severe eosinophilic asthma subgroup for adults and adolescents aged 12 years and older.

Dupilumab is currently investigated in the phase 3 trial, Liberty Asthma VOYAGE, where the study population was children 6 to <12 years of age with a physician diagnosis of persistent asthma for ≥12 months prior to screening and uncontrolled during the screening period, based on clinical history, examination, and pulmonary function parameters according to GINA 2015 Guidelines. This is in line with the target population for dupilumab in the expected EMA indication.

Dupilumab is expected to be placed with other biological drugs that target type 2 inflammation.

Table 4. Description of dupilumab

Subject	Description
Generic name (ATC-code)	Dupilumab (D11AH05)
Mode of action	Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits interleukin-4 and interleukin-13 signalling. Dupilumab inhibits IL-4 signalling via the Type I receptor (IL-4Rα/γc), and both IL-4 and IL-13 signalling through the Type II receptor (IL-4Rα/IL-13Rα). IL-4 and IL-13 are major drivers of human Type 2 inflammatory disease, such as atopic dermatitis, asthma, and CRSwNP. Blocking the IL-4/IL-13 pathway with dupilumab in patients decreases many of the mediators of Type 2 inflammation.
Pharmaceutical form	200mg solution for injection

Posology	The recommended dose of dupilumab for paediatric patients aged 6 to 11 years is according to body weight, as illustrated below:

Body weight	Initial and subsequent dosing
15 to less than 30 kg	300 mg every four weeks (Q4W)
30 kg to less than 60 kg	300 mg every four weeks (Q4W)
60 kg or more	200 mg every other week (Q2W)

Method of administration	Dupilumab is given as a subcutaneous injection
Should the pharamecutical be administered with other medicines	Dupilumab can be used with or without inhaled or oral corticosteroids plus another medicinal product for maintenance treatment.
Treatment duration / Criteria for end of treatment:	Consider end of treatment if unacceptable toxicity, if asthma remains uncontrolled or worsens during treatment.
Necessary monitoring, both during administration and during the treatment period	Dupilumab is intended for long-term treatment. The need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's level of asthma control.
Need for diagnostic or other test	Biomaker for type 2 inflammation

Abbreviations; IL: Interleukin; Q2W: Every 2 week

For efficacy and safety for dupilumab Q4W dosing, see Appendix X.

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

A detailed description of the literature search is provided in **Appendix A Literature search for efficacy and safety of intervention and comparator(s)**. In summary, a global SLR was used as the evidence base for this submission, and was locally adapted to fit the scope of the assessment in Denmark. This approach is deemed feasible as the global SLR was broader and will therefore have included all studies relevant for the scope of this application.

Standard methods for conducting and reporting an SLR were used per the Cochrane Handbook(20, 21) and the PRISMA guidelines(22, 23) to satisfy the requirements of the NICE. The SLR was conducted in February 2021, and the local adaptation was conducted in January 2022.

The local adaptation was conducted to restrict the literature included in the global SLR to international studies with dupilumab, omalizumab or mepolizumab in children with severe asthma. The local adaptation only included internation multicenter studies, while excluding studies with populations not reflective of the Danish patient population. The initial scope of the global SLR was broader and included more studies with populations not relevant for the single technology assessment of dupilumab in Denmark.

Based on the references included at full-text level for the global SLR, Sanofi made a local adaptation to the Danish context, and a total of 5 references from 3 studies was included for this HTA submission, which include data from the Liberty Asthma VOYAGE study, where data was not published at the time of the global SLR.

A full PRISMA diagram outlining the selection process in the global SLR and local adaption is given in **Appendix A Literature search for efficacy and safety of intervention and comparator(s)**.

6.2 List of relevant studies

The relevant studies for alle three subpopulations are listed below in Table 5. Five studies were identified relevant for the three subpopulations for this submission. Details of the study characteristics for each trial can be found **in Appendix B Main characteristics of included studies**.

Table 5. Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
Dupilumab in Children with Uncontrolled Moderate-to-Severe Asthma, L.B. Bacharier, J.F. Maspero, C.H. Katelaris, A.G. Fiocchi, R. Gagnon, I. de Mir, N. Jain, L.D. Sher, X. Mao, D. Liu, Y. Zhang, A.H. Khan, U. Kapoor, F.A. Khokhar, P.J. Rowe, Y. Deniz, M. Ruddy, E. Laws, N. Patel, D.M. Weinreich, G.D. Yancopoulos, N. Amin, L.P. Mannent, D.J. Lederer, and M. Hardin, N Engl J Med, 2021	Liberty Asthma VOYAGE	NCT02948959	April 21, 2017 – August 26, 2020	Dupilumab vs. Placebo for children with uncontrolled moderate-to-severe asthma
Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma, B. Lanier, T. Bridhes, M. Kulus, A.F. Taylor, I. Berhane, C.F. Vidaurre, J Allergy Clin Immunol, 2009	Study IA05	NCT00079937	April 2004 – March 2008	Omalizumab vs. Placebo for children with moderate-to-severe, persistent, inadequately controlled allergic asthma
Omalizumab in children with inadequately controlled severe allergic (IgE-mediated) asthma, M. Kulus, J. Hébert, E. Garcia, C.F. Vidaurre, M. Blogg, Curr Med Res Opin, 2010	Study IA05 (subgroup analysis)	NCT00079937	April 2004 – March 2008	Omalizumab vs. Placebo for children with severe allergic asthma

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
Subcutaneous mepolizumab in children aged 6 to 11 years with severe eosinophilic asthma, A. Gupta, I.P. Pharm, D. Austin, R.G. Price, R. Kempsford, J. Steinfeld, E.S. Bradford,S.W. Yancey, Pediatric Pulmonology, 2019	NA	NCT02377427	August 25, 2015 – January 31, 2018	Mepolizumab in children with severe Eosinophilic asthma
Long-term safety and pharmacodynamics of mepolizumab in children with severe asthma with an eosinophilic phenotype, A. Gupta, M. Ikeda, B. Geng, J. Azmi, R.G. Price, E.S. Bradford, S.W. Yancey, J. Steinfeld, J Allergy Clin Immunol, 2019	NA	NCT02377427	August 25, 2015 – January 31, 2018	Mepolizumab in children with severe Eosinophilic asthma

An open-lable extension study was identified, Liberty Asthma Excursion NCT03560466, but has not been used for this assessment. Assessment of the Safety of Dupilumab in Children with Asthma. One year study to evaluate the long-term safety and tolerability of dupilumab in pediatric patients with asthma who participated in a previous dupilumab asthma clinical study (VOYAGE). This study is still ongoing.

7. Efficacy and safety

7.1 Efficacy and safety of dupilumab compared to omalizumab for treatment of severe allergic asthma in children aged 6 to <12

To evaluate the efficacy and safety of dupilumab versus omalizumab three studies were considered relevant. All studies were both double-blinded RCTs, assessing the efficacy and safety of biological treatment in patients aged 6-11, with placebo as the comparator. Two of the three studies were evaluating the efficacy and safety of omalizumab, one of the studies, Kulus et al. 2010, was a subgroup analysis, which was deemed the relevant patient subgroup for this severe allergic asthma subgroup. The study used data from the study with the full study population, which is why both studies are mentioned, but only the results from the subgroup analysis relevant for this application are reported, except when endpoints was not presented for the subgroup (15, 16).

7.1.1 Relevant studies

7.1.1.1 Liberty Asthma VOYAGE

Liberty Asthma VOYAGE (VOYAGE) is a randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in children 6 to <12 years of age with uncontrolled persistent asthma. Dupilumab was administered subcutaneously (s.c.) every 2 weeks for a 52-week treatment period as add-on therapy to high-dose ICS alone or medium-dose or high-dose ICS in combination with a second controller (e.g., LABA, LAMA, LTRA, or methylxanthines). In the study two primary

efficacy populations were evaluated: the population with the type 2 inflammatory asthma phenotype defined as either baseline blood eosinophil count ≥150 cells per cubic millimeter (mm^3)) or baseline FeNO≥20 parts per billion (ppb), and the population with baseline blood eosinophil count of ≥300 mm^3. A total of 408 patients were enrolled to be randomized to receive dupilumab or placebo.

Patients were randomized in a 2:1 ratio to receive s.c. injection of dupilumab or placebo every two weeks (Q2W). Patients with a body weight at randomization >30 kg received 200 mg dupilumab or the matching placebo Q2W, and patients with a body weight at randomization ≤30 kg received 100 mg dupilumab or the matching placebo Q2W. Due to the different volumes administered with the 100 mg versus the 200 mg doses, two matching placebos were required for this study. Consequently, patients and Investigators were blinded to whether patients were receiving dupilumab or placebo, but not to the dose/volume of the injection (200 mg; 100 mg). After randomization, the assigned weight-tiered dose regimens of dupilumab at randomization were maintained during the treatment period of the study.

Randomization was stratified by ICS dose level (medium, high) at screening, blood eosinophil count (≥150 cells per milimeter (mm^3)) at screening, and region (Latin America, Eastern Europe, and Western countries). Dose levels considered as medium- or high-dose ICS in children 6 to <12 years old were adapted from the GINA guidelines 2015 version (18) that was applicable at the time of study initiation.

A total of 273 children were randomised to receive 100 mg (≤30 kg body weight) or 200 mg (>30 kg body weight) dupilumab subcutaneously Q2W for 52 weeks, of which 268 patients received treatment. Patients and investigators were blinded to whether patients were receiving dupilumab or placebo, but not to the dose/volume of the injection (200 mg; 100 mg). Further, a total of 135 children were randomised to received placebo subcutaneously Q2W for 52 weeks, of which 134 received treatment. Due to the different volumes administered with the 100 mg versus the 200 mg dupilumab doses, two matching placebos were required for this study

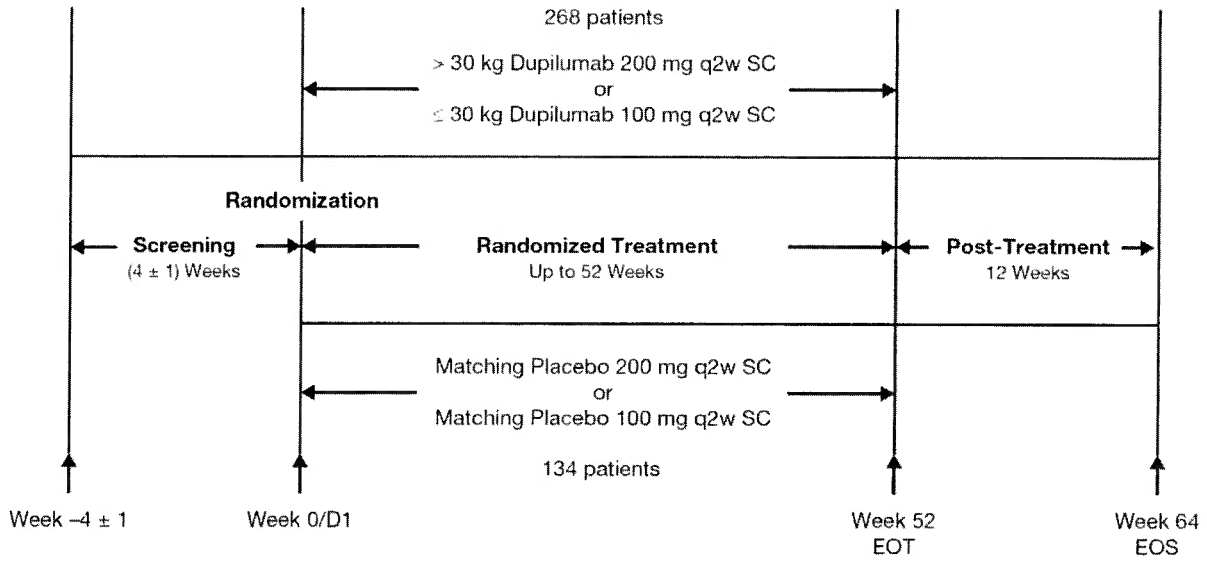
During the randomized treatment period, patients continued taking their background controller medication(s) at the stable dose used during the screening period. Patients requiring a third controller medication for their asthma were

not considered eligible for this study. Patients were allowed to use albuterol/salbutamol or levalbuterol/levosalbutamol as reliever medication as needed during the study.

The study consisted of 3 periods with a total duration of 68 ± 1 weeks for each patient (Figure 6):

- Screening period (4 ± 1 weeks);
- Randomized double-blind treatment period (up to 52 weeks) during which patients received dupilumab or placebo administered as s.c. injections;
- And, post-treatment period (12 weeks) for patients who did not participate in the 1-year long-term extension study (LTS14424).

Figure 6. Study design – ITT population



Notes: Background medication: medium dose ICS + second controller or high dose ICS alone or + second controller
D: day; EOT: end of treatment; EOS: end of study; ICS: inhaled corticosteroids; Q2W: every 2 week; R: randomization; s.c.: subcutaneous

The primary outcome of the study was annualized rate of severe exacerbation events, with secondary outcomes concerning respiratory functioning and patient related outcome measures. Furthermore, the safety profile of dupilumab in children in the age of 6 to <12 years was investigated by evaluation the AEs and SAEs.

Main inclusion criteria were patients from 6 to <12 years of age, with a physician diagnosis of persistent asthma for ≥12 months prior to screening based on clinical history and examination, pulmonary function parameters according to GINA 2015 Guidelines and the following criteria:

- Existing background therapy of medium-dose ICS with second a controller medication (i.e., LABA, LTRA, LAMA, or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller, for at least 3 months with a stable dose ≥1 month prior to Screening Visit 1 (dose levels as per 16-1-1-amended3 [Appendix A]).
- Pre-bronchodilator forced expiratory volume in 1 second (FEV1) ≤95% of predicted normal or pre-bronchodilator FEV1/forced vital capacity (FVC) ratio <0.85 at screening and baseline visits.
- Reversibility of at least 10% in FEV1 after the administration of 200 to 400 mcg (2 to 4 puffs with metered-dose inhaler [MDI]) of albuterol/salbutamol or 45 to 90 mcg (2 to 4 puffs with MDI) of levalbuterol/levosalbutamol reliever medication before randomization (up to 3 opportunities during the same visit were allowed

The complete overview of study characteristics, along with outcomes and in- and exclusion criteria can be found in Table 88 in the Appendices.

7.1.1.1.1 Dupilumab subgroup covering the population with severe allergic asthma

The Liberty Asthma VOYAGE trial had broad eligibility criteria, and patients were not selected for enrolment based on phenotypic traits. In order to cover this patient population, a subgroup analysis have been conducted using data from the Liberty Asthma VOYAGE trial, defined as:

- **Allergic asthma subgroup**: This subgroup included patients with allergy, defined as baseline total IgE ≥30 IU/mL and at least one perennial allergen or one seasonal allergen specific IgE value ≥0.35 IU/mL at baseline

The baseline characteristics of the subgroup is presented in Table 91.

7.1.1.2 IA05 Study (omalizumab)

IA05 is a randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of omalizumab in children with moderate-to-severe persistent allergic asthma that was inadequately controlled despite treatment with medium-dose or high-dose inhaled corticosteroids (ICSs) with or without other controller medications (15).

Patients included in the study was children from 6 to <12 years of age who was diagnosed with moderate-to-severe allergic (immunoglobulin E (IgE)-mediated) asthma, see Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety for further patient characteristics. Patients were randomly assigned 2:1 to receive either omalizumab or placebo. Omalizumab was administered once or twice a month by s.c. injection consisting of 75 to 375 mg omalizumab as determined from dosing tables, based on baseline IgE total serum and body weight. The double-blind treatment period consisted of a 24-week fixed-steroid phase (constant ICS dose unless adjustment was required for an exacerbation) and a 28-week adjustable-steroid phase where doses could be adjusted downward if patients met a strict criterion for steroid reduction (15).

The main criteria for inclusion were patients in the age of 6 to <12 with moderate-to-severe allergic (IgE-mediated) asthma and the following criteria:

- Had inadequately controlled asthma despite receiving at least medium doses of ICS (≥200 mg/d fluticasone propionate via dry powder inhaler or equivalent)
- Had daytime or night-time symptoms
- Demonstrated an increase of ≥12% in FEV_1 after 4 puffs (4 X 100 µg) or up to 5 mg nebulized albuterol
- Had a history of exacerbations (≥2 within 1 year, ≥3 within 2 years, or ≥1 severe exacerbation requiring hospitalization within 1 year before study entry).
- To weigh between 20 and 150 kg
- Have a positive skin prick test result to at least 1 perennial allergen and/or a positive radioallergosorbent test, and have a total serum IgE level of 30 to 1,300 IU/mL.

The complete overview of study characteristics, along with outcomes and in- and exclusion criteria can be found in

Table 89 in **Appendix B Main characteristics of included studies**.

The majority of children with asthma is atopic, and mean serum IgE is often high in children with severe asthma, leading to a strong rationale for investigating anti-IgE therapy in this population. A study by *Kulus et al. 2010* made a pre-specified subgroup analysis conducted using data from the large randomized, double-blind, placebo-controlled, parallel-group study by Lanier et al. 2009 reported above (15, 16). This analysis focused on the subgroup of children with inadequately controlled severe asthma, despite receiving high-dose ICS (≥500 mg · day-1 FP or equivalent) and a LABA, with or without other controller medications (16). The analysis included 246 randomised patients (omalizumab, n = 166; placebo, n = 80), of which 159 received treatment with omalizumab and 76 received placebo. Results from this study will be presented in section 7.1.27.1.2.

The primary efficacy endpoint was the rate of clinically significant asthma exacerbations, defined as worsening of asthma symptoms required doubling of baseline ICS dose and/or treatment with rescue systemic corticosteroids for ≥3 days) over a period of 24 weeks (end of the fixed-steroid treatment phase).

Secondary endpoint included:

- Rate of clinically significant asthma exacerbation rate during the 52 weeks treatment period.

Exploratory efficacy endpoints included:

- Percentage reduction in ICS dose during the 28-week steroid-adjustable phase
- Rate of severe asthma exacerbations over periods of 24 and 52 weeks (28-week adjustable-steroid phase)
- Rate of clinically significant exacerbations over 52 weeks in patients with baseline percent predicted FEV_1 <80% and ≥80%
- Physicians' global evaluation of treatment effectiveness (GETE) at 52 weeks.

Safety assessments consisted of the recording of all AEs, physical examinations, medical history, vital signs, and any clinically significant changes in laboratory values (15).

Table 6. Study characteristics for included studies

	Liberty Asthma VOYAGE	Omalizumab (IA05)
Study design	Randomized, double-blind, placebo-controlled phase 3	Randomized, double-blinded, placebo-controlled phase 3
Intervention	Dupilumab	Omalizumab
Comparator	Placebo	Placebo
Population	Children (6 to <12 years) with uncontrolled persistent asthma	Children (6 to <12 years) with moderate-severe, inadequately controlled allergic asthma
Stratification	• Eosinophilic asthma (Blood eosinophils ≥ 300 cells/µL)	• IgE-mediated asthma

	Liberty Asthma VOYAGE	Omalizumab (IA05)
	• Allergic asthma (Type 2 inflammatory asthma phenotype, EOS≥ 150 cells/µL or FeNO ≥20 ppb)	
Primary endpoint	Asthma exacerbation rate during the 52-week treatment period	Asthma exacerbations
Secondary endpoints	• Pre-bronchodilator % predicted FEV_1 • ACQ-7-IA • FeNO level • Time to first severe exacerbation • Time to first LOAC • Number of puffs of reliever medication • PAQLQ(S)	• Asthma exacerbation rate 52 weeks treatment period • % reduction of ICS dose • Asthma exacerbations over 52 weeks in patients with baseline percent predicted FEV_1 <80% and ≥80% • Physician GETE • Rate of severe asthma exacerbations
Longest follow-up time	52 weeks	52 weeks

Abbreviations; FEV_1: Forced Expire Volume in the first second; ACQ-7-IA: Asthma Control Questionnaire 7 interviewer-Administrated version; FeNO: Fractional exhaled nitric oxide; LOAC: Loss of Asthma Control; PAQLQ: Paediatric Asthma Quality of Life Questionnaire; IgE: immunoglobulin E; ICS: Inhaled Corticosteroids; GETE: Global evaluation of treatment effectiveness

7.1.2 Efficacy and safety – results per study

The relevant study outcomes presented for dupilumab are based on the Liberty VOYAGE study for the population of severe allergic asthma and the outcomes presented for omalizumab are primarily based on the study by Kulus et al. 2010, as this study includes the population of interest for this subgroup, children aged 6 to <12 years diagnosed with severe allergic asthma, although results from Lanier et al., 2009(15), have included quality of life endpoints. In the SLR, it was identified that heterogeneity with respect to study design, inclusion criteria, outcomes definition, and the lack of reporting of key baseline characteristics would likely present barriers in terms of the comparability of studies.

7.1.2.1 Results – LIBERTY VOYAGE

7.1.2.1.1 Efficacy results, dupilumab

Number of severe exacerbation events

Over a 52 weeks treatment period, 115 patients with severe allergic asthma were treated with dupilumab and 63 patients receiving matching placebo. The annualized rate of severe exacerbation events during the 52 week treatment period was [redacted] n the dupilumab arm [redacted] in the placebo arm resulting in an absolute difference of [redacted] and a statistically significant relative risk difference of [redacted] the dupilumab-arm compared to placebo, Table 7 (24).

[redacted] f the patients in the dupilumab-arm did not experience a severe exacerbation during the 52-week treatment duration, while a small proportion of patients ([redacted] of the patients in the placebo-arm experienced no exacerbation during the same period. The difference exceeds the minimally clinical important difference (MCID) of 10% presented in the treatment guidelines for severe asthma by the DMC(50).

Change from baseline in ppFEV1% to week 12

The predicted pre-bronchodilator ppFEV1 was measured at baseline to a mean ppFEV1 (SD±) of [redacted] in the dupilumab group and [redacted] in the placebo group. In week 12, the change from baseline was estimated [redacted] and [redacted] for the dupilumab group and placebo group. Dupilumab showed a significant LSmean difference of [redacted] compared to placebo in the Liberty Asthma VOYAGE-trial.

Percentage of patients with ≥200mL improvement in FEV1 at week 12

At week 12, numerically a higher proportion of patients in the dupilumab group had an improvement in FEV1 of 200 mL or more [redacted] more patients) when compared to placebo.

Asthma control

Asthma control was assessed by the use of ACQ-7-IA in Liberty Asthma VOYAGE. ACQ-7-AI score were measured at baseline and at week 24. The LSmean ACQ-7-AI change from baseline in week 24 showed a greater reduction indicating a better asthma control in the dupilumab group [redacted] in the placebo group, and dupilumab showed a statistically significant improvement [redacted] compared to placebo.

Quality of life

Quality of life was assessed using the PAQLQ-IA tool in Liberty Asthma VOYAGE. Compared to placebo, dupilumab showed a statistically significant mean improvements in asthma health related quality of life as measured by change from baseline (indicated by higher scores on the PAQLQ-IA) in PAQLQ-IA global score over time of [redacted] at week 52.

In the PRQLQ global score, dupilumab showed a significant mean improvement over time (indicated by lower score on the PRQLQ) [redacted] at week 52 compared to placebo.

Table 7. Summary of study results dupilumab, children with severe allergic asthma, efficacy outcomes

Outcome	Dupilumab (n=115)	Placebo (n=63)	AD (95% CI)	RD (95% CI)	p-value
Efficacy results					
Annualized rate of severe asthma exacerbations during 52-week treatment period (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

% Experience no exacerbation during 52-week treatment periods, % (95% CI)	[redacted]
Change from BL at week 12 of ppFEV1, (±SE)	[redacted]
% patients with >=200mL improvement in FEV1 at week 12 (95% CI)	[redacted]
Change from BL at week 24 of ACQ-7-IA, (±SE)	[redacted]
Change from BL at week 52 of PAQLQ-IA global score (+SE)	[redacted]
Change from BL at week 52 of PRQLQ global score (+SE)	[redacted]

Abbreviations: AD, absolute difference; BL, base line; CI, Confidence Interval; NA, not available; ppFEV1, predicted prebronchodilator FEV1; RD, relative difference. **Note**: #, p-value for RD; *, p-value for AD.

For a table showing summary of study results dupilumab, children with type 2 inflammation asthma, see Appendix V.

7.1.2.1.2 Safety results, dupilumab

Safety data for dupilumab were only reported for the safety population that included all the patients who received ≥1 dose or part of a dose, and data were analysed according to the intervention received. All reported AEs below are treatment emergent AEs (TEAE) See Table 8 for the summary of safety outcomes.

The overall incidence of adverse events during the trial period were similar between groups in the safety population, Table 8. SAEs were reported in 13 patients [redacted] in the dupilumab group and in 6 [redacted] in the placebo group. (24). The difference was not statistically significant.

Few patients discontinued treatment due to adverse events in Liberty Asthma VOYAGE. The discontinuation rate due to AE were [redacted] for patients treated with dupilumab [redacted] for the patients treated with placebo(24). Most of TEAEs that led to discontinuation occurred in only 1 patient each in any given treatment group. Injection site erythema and injection site oedema leading to treatment discontinuation were both reported in 2 patients in the dupilumab group versus none in the placebo group. Both cases were severe injection site reactions lasting for at least 24 hours and meeting the AESI criteria. Two patients experienced neutropenia leading to permanent treatment discontinuation: one of them in the placebo group and the other in the dupilumab group. Both patients recovered. All adverse event related discontinuations are summarised in Table 101 in **Appendix E Safety data for intervention and comparator(s)**.

AEs of special interest, includes eosinophilia, which occurred [redacted] of the patients in the dupilumab and placebo groups, respectively. Most episodes of eosinophilia were self-limited laboratory findings without any associated symptoms. A single case of eosinophilia was associated with clinical symptoms that included hospitalization and permanent discontinuation of dupilumab. Parasitic infections were reported in 7 patients ([redacted] the dupilumab group. All cases of parasitic infections were mild, and

all the patients recovered after treatment with anthelmintic therapy with no permanent discontinuation of dupilumab or placebo. The incidence of conjunctivitis was low in both groups; one case of keratitis was reported in each group. There were no deaths during the trial. Antidrug antibody responses were observed [redacted] of the patients in the dupilumab group and [redacted]% of those in the placebo group.

A list of frequent adverse event and adverse events of special interest is provided in Table 9.

Table 8. Summary of study results dupilumab, safety population, safety outcomes

Outcome	Dupilumab (n=271)	Placebo (n=134)	AD (95% CI)	RD (95% CI)	p-value
Safety results					
AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD, absolute difference; CI, Confidence Interval; AE, Adverse event; SAE, Severe adverse events. **Note**: #, p-value for RD; *, p-value for AD.

Table 9. Most frequent treatment emergent adverse events <5% and adverse event of special interest in the LIBERTY VOYAGE Study

Most frequent AEs, n (%)		Dupilumab (n=271)	Placebo (n=134)
Nasopharyngitis		50 (18.5)	29 (21.6)
Upper respiratory tract infection	Any	35 (12.9)	18 (13.4)
	Viral	33 (12)	3 (9.7)
Pharyngitis		24 (8.9)	14 (10.4)
Influenza		20 (7.4)	12 (9.0)
Bronchitis		17 (6.3)	14 (10.4)

Sinusitis		9 (3.3)	7 (5.2)
Eosinophilia‡		16 (5.9)	1 (0.7)
Allergic rhinitis		16 (5.9)	16 (11.9)
Cough		15 (5.5)	9 (6.7)
Accidental overdose§		3 (1.1)	7 (5.2)
Injection-site reaction¶	Erythema	35 (12.9)	13 (9.7)
	Edema	28 (10.3)	7 (5.2)
	Nodule	17 (6.3)	3 (2.2)
Adverse events of special interest			
Anaphylactic reaction		[redacted]	[redacted]
Hypersensitivity (medically review)		[redacted]	[redacted]
Serious injection site reaction or severe injection site reaction that last longer than 24 hours		[redacted]	[redacted]
Severe or serious infection		[redacted]	[redacted]
Parasitic infection		[redacted]	[redacted]
Opportunistic infection		[redacted]	[redacted]
Potentially drug-related liver disourder		[redacted]	[redacted]

‡ Eosinophilia was defined as a peripheral-blood eosinophil count at least 3000 cells per cubic millimeter.
§Overdose was defined as at least twice the standard dose of either dupilumab or placebo during an interval of less than 11 days.
¶Descriptions of injection-site reactions include MedDRA high-level terms.

7.1.2.2 Results – Omalizumab, IA05

7.1.2.2.1 Efficacy results, IA05

Number of exacerbation events

The rate of clinically significant asthma exacerbations was observed to be significantly lower in omalizumab-treated patients than in the placebo group (0.42 vs 0.63) over the 24-week period. The rate ratio (RR) of omalizumab vs. placebo was 0.662 (0.441 - 0.995, p=0.047).

During the 52-week treatment period, the rate of clinically significant asthma exacerbations was observed to be 0.73 in omalizumab-treated patients and 1.44 in placebo-treated patients, resulting in a RR of 0.504 (0.350 - 0.725, p<0.001).

Over the 28-week adjustable-steroid phase (Weeks 25 to 52), the rate of clinically significant asthma exacerbations was 0.29 in omalizumab treated patients and 0.77 in placebo treated patients, resulting in a RR of 0.372 (0.243 – 0.568, p<0.001).

During the 52 week-period, the rate of clinically significant exacerbations was significantly reduced in patients with baseline percent predicted FEV1 <80%, 0.84 vs 1.64 (RR: 0.512 (0.315 - 0.833, p=0.007)) and in those with baseline percent predicted FEV_1 ≥80%, 0.66 vs 1.35 (RR: 0.488 (0.279 – 0.853, p=0.012)) when compared to placebo.

Quality of life

Quality of life was assessed using the PAQLQ-IA in the Lanier et al., 2009(15), however, no subgroup data was presented in the Kulus et al., 2010(16). Therefore, data is instead presented for the complete population from Lanier et al., 2009. No significant difference was observed between the omalizumab-arm and the placebo-arm at week 24 (Least squares mean difference 0.04 in favour of omalizumab (p = 0.676)).

Table 10. Summary of study results omalizumab, efficacy outcomes, IA05 (Kulus et al., 2010(16))

Outcome	Omalizumab (n=159)	Placebo (n=76)	AD (95% CI)	RD (95% CI)	p-value
Efficacy results					
Clinically significant asthma exacerbation rate, week 0-24	0.42	0.63	21.02 (7.72-34.31)	0.662 (0.441 - 0.995)	0.002* 0.047#
Clinically significant asthma exacerbation rate, week 0-52	0.73	1.44	0.71 (0.59-0.83)-	0.504 (0.350 - 0.725)	<0.001* <0.001#
Clinically significant asthma exacerbation rate, week 25-52	0.29	0.77	0.48 (0.36-0.60)	0.372 (0.243, 0.568)	<0.001* <0.001#
Rate of clinically significant exacerbations over 52 weeks in FEV_1 <80%	0.84	1.64	0.80 (0.64-0-96)	0.512 (0.315, 0.833)	<0.001*

patients with baseline percent predicted FEV_1 <80% and ≥80%						0.007#
	FEV_1 ≥80%	0.66	1.35	0.69 (0.59-079)	0.488 (0.279, 0.854)	<0.001* 0.012#
Change from BL at week 24 of PAQLQ-IA global score*		NA	NA	0.04	NA	0.676*

Abbreviations: AD, absolute difference; BL, base line; CI, Confidence Interval; NA, not available; RD, relative difference. **Note:** #, p-value for RD; *, p-value for AD. **Note:** *, Data from Lanier et al., 2009(15) . **Note:** #, p-value for RD; *, p-value for AD.

7.1.2.2.2 Safety results, IA05

The safety of omalizumab was evaluated in the IA05 trial. Patients had a mean exposure to omalizumab, or placebo was 49.8 and 49.1 weeks, respectively, and 93% of patients completed at least 28 weeks on omalizumab. The overall incidence of AEs was similar in both groups (Table 11).

The overall incidence of SAEs was lower in the omalizumab group compared to the placebo group (3.6% vs 10.0%), Table 11. Few patients experienced pre-specified changes in laboratory values (one omalizumab patient in the EU safety population had a transient low platelet count, but this had returned to normal on re-testing, with no associated bleeding disorders) and overall rates were similar in both groups.

Pyrexia was the only AE that occurred with a frequency >5% higher in the omalizumab group (18.7%) than in the placebo group (8.8%), but this difference was not statistically significant (P=0.059), see Table 12. Upper respiratory tract infection, sinusitis, viral upper respiratory tract infection, and streptococcal pharyngitis were more frequent in the placebo group (>5%) than in the omalizumab group, Table 12.

Table 11. Summary of study results Omalizumab, safety outcomes, IA05 (Kulus et al., 2010(16))

Outcome	Omali-zumab (n=166)	Placebo (n=80)	AD (95% CI)	RD (95% CI)	p-value
Safety results					
AEs, n (%)	155 (93.4)	76 (95.0)	-1.63% (-7.72% - 4.47%)	0.98 (0.92 - 1.05)	0.6132* 0.6125#
AEs leading to discontinuation, n (%)	2 (1.2)	0 (0.0)	1.20% (-0.45% - 2.86%)	2.42 (0.12 - 49.77)¤	0.1553* 0.5791#¤
SAE	6 (3.6)	8 (10.0)	-6.39% (-13.55% - 0.78%)	0.36 (0.13 - 1.01)	0.0801* 0.0511#

Abbreviations: AD, absolute difference; CI, Confidence Interval; AE, Adverse event; SAE, Severe adverse events. **Note**: #, p-value for RD; *, p-value for AD; ¤, 0.5 added to all cells in 2x2, to calculate relative differences as 0 events occurred in placebo arm.

Table 12. Most frequent AEs reported in the Omalizumab study, IA05 (Kulus et al., 2010(16))

Most frequent AEs, n (%)	Omalizumab (n=166)	Placebo (n=80)
Nasopharyngitis	49 (29.5)	20 (25.0)
Upper respiratory tract infection	40 (24.1)	28 (35.0)
Sinusitis	36 (21.7)	23 (28.8)
Pyrexia	31 (18.7)	7 (8.8)
Cough	27 (16.3)	12 (15.0)
Headache	24 (14.5)	12 (15.0)
Pharyngolaryngeal pain	21 (12.7)	10 (12.5)
Vomiting	19 (11.4)	10 (12.5)
Bronchitis	19 (11.4)	12 (15.0)
Viral upper respiratory tract infection	12 (7.2)	11 (13.8)
Pharyngitis, streptococcal	11 (6.6)	11 (13.8)

Abbreviations; AE: Adverse events

7.1.3 Comparative analyses of efficacy and safety

Due to the heterogeneity between the two studies, as well as lack of comparable endpoints, a narrative comparison has been conducted on the outcomes where possible. Although, an indirect treatment comparison was deemed unfeasible due to the heterogeneity of the studies an exploratory Bucher ITC has been conducted and is presented in Appendix F Comparative analysis of efficacy and safety.

7.1.3.1 Number of exacerbations

No common outcomes or common outcome definitions were identified between the Liberty Asthma VOYAGE-trial and the IA05-trial. The definition of severe exacerbations in VOYAGE was asthma requiring systemic corticosteroids for ≥3 days or hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids, while IA05 defined a clinically significant exacerbation as worsening of asthma symptoms requiring systemic corticosteroids for ≥3 days or doubling of baseline ICS dose. These differences in definition together with the heterogeneity in study design, inclusion criteria etc., present barriers in terms of the comparability of the studies. Therefore, results are compared using a narrative synthesis.

Results from Liberty Asthma VOYAGE indicate that dupilumab significantly reduces the risk of severe exacerbations compared to placebo by 56% in patient with severe allergic asthma. A higher proportion of patient in the dupilumab group did not experience an exacerbation during the 52-week follow-up period compared to placebo in the trial.

Results from IA05 indicate that omalizumab significantly reduces the number of clinically significant asthma exacerbations compared to placebo in the IA05-trial. Omalizumab showed significant risk reduction throughout all presented exacerbation outcomes presented in the IA05-publication(16).

Both studies indicate that dupilumab and omalizumab reduce the risk of exacerbations significantly compared to placebo, although demonstrated in different exacerbation definitions. It is therefore not possible to conclude that dupilumab is superior to omalizumab in reducing severe exacerbation in severe allergic asthma patients.

Table 13. Summary of exacerbation-related outcomes in Liberty Asthma VOYAGE and IA05 (Kulus et al., 2010(16))

Study/outcome		Intervention arm	Comparator arm	AD (95% CI)	RD (95% CI)	p-value
Liberty Asthma VOYAGE		**Dupilumab (n=271)**	**Placebo (n=134)**			
Annualized rate of severe asthma exacerbations during 52-week treatment period (95% CI)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% Experience no exacerbation during 52-week treatment periods, %		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IA05 (Kulus et al., 2010)		**Omalizumab (n=166)**	**Placebo (n=80)**			
Clinically significant asthma exacerbation rate, week 0-24		0.42	0.63	NA	0.662 (0.441 - 0.995)	0.047#
Clinically significant asthma exacerbation rate, week 0-52		0.73	1.44	NA	0.504 (0.350 - 0.725)	<0.001#
Clinically significant asthma exacerbation rate, week 25-52		0.29	0.77	NA	0.372 (0.243, 0.568)	<0.001#
Rate of clinically significant exacerbations over 52 weeks in patients with baseline percent predicted FEV_1 <80% and ≥80%	**FEV_1 <80%**	0.84	1.64	NA	0.512 (0.315, 0.833)	0.007#
	FEV_1 ≥80%	0.66	1.35	NA	0.488 (0.279, 0.854)	0.012#

Abbreviations: AD, absolute difference; CI, Confidence Interval; NA, not available; ppFEV1, predicted prebronchodilator FEV1; RD, relative difference. **Note:** #, p-value for RD; *, p-value for AD.

7.1.3.2 Change from baseline in ppFEV1% to week 12

This endpoint has only been reported for dupilumab in the Liberty Asthma VOYAGE-trial, please see section 7.1.2.1.1. No data is available for omalizumab on this endpoint.

7.1.3.3 %-patients with >=200mL improvement in FEV1 at week 12

This endpoint has only been reported for dupilumab in the Liberty Asthma VOYAGE-trial, please see section 7.1.2.1.1. No data is available for omalizumab on this endpoint.

7.1.3.4 Asthma control

This endpoint has only been reported for dupilumab in the Liberty Asthma VOYAGE-trial, please see section 7.1.2.1.1. No data is available for omalizumab on this endpoint.

7.1.3.5 Quality of life

It was not possible to perform a statistical indirect comparison, due to the heterogenic nature of the two studies, and data for the omalizumab study was scarce. A non-statistically significant absolute difference in change from baseline in PAQLQ-IA global score of 0.04 point was reported in favour of the omalizumab arm in the Lanier et al.-trial. A significant absolute difference in change from baseline in PAQLQ-IA global score at week 52 of [redacted] was estimated in favour the dupilumab arm in Liberty Asthma VOYAGE. Based on this narrative comparison, it is highly likely that dupilumab is at par with omalizumab, if not superior in terms of the patient's quality of life while on treatment. However, due to the differences in study design, inclusion criteria and follow-up period, this comparison should be interpreted with caution.

Study/outcome	Intervention arm	Comparator arm	AD (95% CI)	RD (95% CI)	p-value
Liberty Asthma VOYAGE	**Dupilumab (n=271)**	**Placebo (n=134)**			
Change from BL at week 52 of PAQLQ-IA global score (+SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lanier et al., 2009	**Omalizumab (n=166)**	**Placebo (n=80)**			
Change from BL at week 24 of PAQLQ-IA global score*	NA	NA	0.04 (NA)	NA	0.676*

Abbreviations: AD, absolute difference; BL, base line; CI, Confidence Interval; NA, not available; ppFEV1, predicted prebronchodilator FEV1; RD, relative difference. **Note:** #, p-value for RD; *, p-value for AD.

7.1.3.6 Safety outcome

Proportion of patients with serious adverse events

As it was not possible to perform statistical indirect comparison, due to the heterogenic nature of the two studies, a narrative comparison between the two studies will be conducted instead. In both studies, the risk of having an SAE were similar between the biologic intervention arms and the placebo arms, albeit small differences were observed. However, none of the differences were statically significant. Based on this narrative comparison, it is unlikely to expect significant differences between dupilumab and omalizumab in terms of risk of SAE. (See Table 14)

Table 14. Summary of proportion with serious adverse events – Liberty Asthma VOYAGE vs. IA05 (Kulus et al., 2010(16))

Study/outcome	Intervention arm	Comparator arm	AD (95% CI)	RD (95% CI)	p-value
Liberty Asthma VOYAGE	**Dupilumab (n=271)**	**Placebo (n=134)**			
SAE	13 (4.8)	6 (4.5)	0.32% (-4.01% - 4.65%)	1.07 (0.42 - 2.76)	0.8937* 0.8950#
IA05 (Kulus et al., 2010)	**Omalizumab (n=166)**	**Placebo (n=80)**			
SAE	6 (3.6)	8 (10.0)	-6.39% (-13.55% - 0.78%)	0.36 (0.13 - 1.01)	0.0801* 0.0511#

Abbreviations: AD, absolute difference; CI, Confidence Interval; SAE, Severe adverse events. **Note**: #, p-value for RD; *, p-value for AD.

Proportion of patients discontinued due to adverse events

In both studies, the risk of discontinuation due to AEs were similar between the two arms in the Liberty Asthma VOYAGE -trial, while larger numerical differences were observed in the IA05-trial between the omalizumab-arm and the placebo-arm. However, none of the differences between the biologic intervention-arms and the placebo-arms were statistically significant. (See Table 15)

Table 15. Summary of proportion of patients discontinued due to adverse events – Liberty Asthma VOYAGE vs. IA05 (Kulus et al., 2010(16))

Outcome	Intervention arm	Comparator arm	AD (95% CI)	RD (95% CI)	p-value
Liberty Asthma VOYAGE	**Dupilumab (n=271)**	**Placebo (n=134)**			
AEs leading to discontinuation, n (%)	5 (1.8)	2 (1.5)	0.35% (-2.25% - 2.96%)	1.24 (0.24 - 6.29)	0.8029* 0.8103#
IA05 (Kulus et al., 2010)	**Omalizumab (n=166)**	**Placebo (n=80)**			
AEs leading to discontinuation, n (%)	2 (1.2)	0 (0.0)	1.20% (-0.45% - 2.86%)	2.42 (0.12 - 49.77)¤	0.1553* 0.5791#¤

Abbreviations: AE, Adverse event; AD, absolute difference; CI, Confidence Interval; SAE, Severe adverse events.

7.2 Efficacy and safety of dupilumab compared to mepolizumab for treatment of severe eosinophilic asthma in children aged 6 to <12

To evaluate the efficacy and safety of dupilumab versus mepolizumab two studies were considered relevant. The two studies were both assessing the efficacy and safety of a biological treatment in patients aged 6-11 with severe eosinophile asthma.

7.2.1 Relevant studies

7.2.1.1 Liberty Asthma VOYAGE

The Liberty Asthma VOYAGE trial had broad eligibility criteria, and patients were not selected for enrolment based on phenotypic traits. In order to cover this patient population, a subgroup analysis have been conducted using data from the Liberty Asthma VOYAGE trial, defined as:

- **Severe eosinophilic asthma**: This subgroup included patients with baseline blood EOS ≥150 cells/µL.

Please consult section 7.1.1.1 for a description of the study and Table 16 for a comparison of study characteristics Liberty Asthma VOYAGE and the mepolizumab children-trial.

Full study characteristics are presented in **Appendix B Main characteristics of included studies**. A comparison of patient baseline characteristics between the subgroup in Liberty Asthma VOYAGE and the mepolizumab children-trial is presented in the appendices in Table 92.

7.2.1.2 Mepolizumab – children trial (NCT02377427)

The mepolizumab trial is an open-label, non-controlled repeat-dose phase 2 trial conducted in children with severe asthma with an eosinophilic phenotype. Participants were children aged 6 to 11 years with a diagnosis of severe asthma, as defined by regional guidelines, and eosinophilic airway inflammation demonstrated by peripheral blood eosinophil counts ≥300 cells/µL within 12 months of screening or ≥150 cells/µL at screening. Eligible children had also experienced ≥2 exacerbations requiring treatment with systemic corticosteroids (SCS) ≤ 12 months before screening (an exacerbation in children receiving maintenance OCS must have necessitated a ≥twofold increase in their OCS dose). Another criteria for inclusion were that participants 12 months before screening, were receiving regular medium- or high-dose ICS (>200 µg/day fluticasone propionate or equivalent) with or without maintenance OCS. They were also receiving ≥1 additional controller medication (e.g., long-acting β-2-agonist, leukotriene receptor antagonist, or theophylline) for ≥3 months, or had a documented failure of the additional controller medication for ≥3 successive months, in the 12 months before screening, see Appendix B Main characteristics of included studies and Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety for further information regarding inclusion-/exclusion criteria and patient characteristics. The trial was conducted at 13 centres in Japan, Portland, UK, and United states (18, 51).

The study design consisted of two parts to characterize the pharmacokinetics (PK), pharmacodynamics (PD), safety, and efficacy of mepolizumab in children 6 to 11 years of age with severe asthma with an eosinophilic phenotype, a 2-part study, Figure 7 and Table 16.

Part A

In Part A the PK and PD of mepolizumab was assessed. Children received mepolizumab subcutaneous (s.c.) once every 4 weeks for a total of three doses (week 0, 4, and 8) in the active treatment period of week 0 to 12. Based on the patients weight at baseline, they were assigned to receive a dose of 40mg if they weighed <40 kg or at 100mg if they weighed ≥40 kg (18). In the assessment for eligibility 44 children were identified. Of these 44 children 36 were included to partake of the part A, where 26 received 40mg of mepolizumab and 10 received 100mg mepolizumab (18).

The primary endpoints in the trial were the PK and PD of mepolizumab. The PK model derived estimates of mepolizumab plasma clearance, area under the plasma concentration-time curve to infinity ($AUC_{[0\text{-}inf]}$), maximum plasma concentration (C_{max}), and terminal phase elimination half-life ($t_{1/2}$). The primary PD endpoint was the ratio of absolute blood eosinophil count at week 12 to baseline (18).

Secondary endpoints included bodyweight-adjusted plasma clearance estimates, change from baseline in Asthma Control Questionnaire 7-item (ACQ-7) score and Childhood Asthma Control Test (C-ACT) score, both at weeks 4, 8, 12, 16, and 20. Mepolizumab safety and tolerability were assessed through adverse event (AE) reporting, immunogenicity, laboratory parameters, and vital signs (18).

Exploratory endpoints included asthma exacerbation frequency during the treatment period (weeks 0–12) and throughout part A (weeks 0–20), change from baseline to week 12 in FEV1 and serum total IL-5 levels. An exacerbation was defined as worsening of asthma that required s.c. treatment and/or hospitalization and/or an emergency room (ER) visit (18).

Part B

In Part B of the study, assessment of the long-term safety and PD of mepolizumab over a 52-week treatment period was conducted (72-weeks including part A). Children who completed all doses and assessments in the part A of the trial were given the option to continue receiving mepolizumab in part B. In this part of the trial children were recommended to receive further 13 doses of mepolizumab (17). 36 children were included in the part A of the trial. Of these 36 children, 30 (83%) consented to continue in part B. Two eligible children decided not to enter part B and four children were not eligible due to no completion of part A (51).

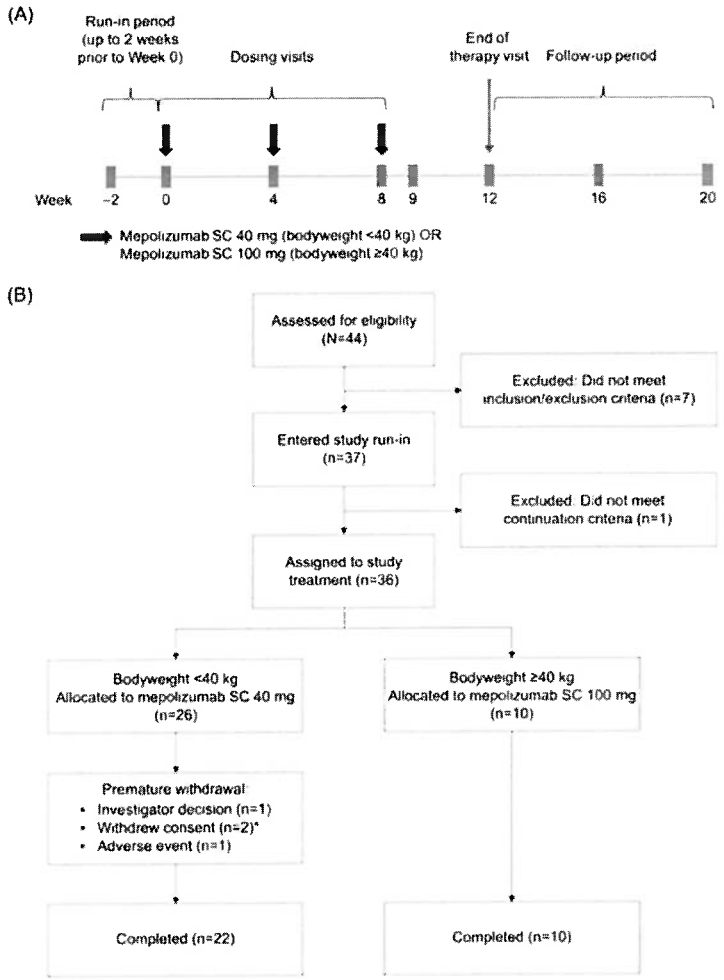
The primary endpoint of the part B in the trial were the incidence of AEs (On-treatment, posttreatment, serious adverse events (SAE), and adverse AE of special interest (AESIs)), clinically significant changes in vital sign measurements and laboratory parameters, and the frequency of positive anti-mepolizumab binding antibodies and neutralizing antibodies (51).

To characterize the long-term pharmacodynamics of mepolizumab, the secondary end point of absolute blood eosinophil count (cells per microliter) was recorded at overall study weeks 32, 44, 56, 68, and 72 and follow-up week 80 (51).

Exploratory end points included asthma exacerbation frequency over the treatment period plus changes from baseline in Asthma Control Questionnaire, 7-item (ACQ-7) or 5-item (ACQ-5), and Childhood Asthma Control Test (C-ACT) scores at overall study weeks 32, 44, 56, 68, 72, and 80 (51).

Annualized exacerbation rates were compared with those calculated over the 12 months preceding mepolizumab administration in part A.

Figure 7. Study design, Mepolizumab



Note; Part A study (A) design and (B) patient flow. *Consent was withdrawn for one child during the follow-up period after receiving all three doses of study treatment. s.c., subcutaneous

Table 16 Study characteristics for included studies in eosinophilic asthma

	Liberty Asthma VOYAGE	Mepolizumab-trial (NCT02377427)
Study design	Randomized, double-blind, placebo-controlled phase 3	Non-randomized, open-label, interventional study
Intervention (n patients)	Dupilumab	Mepolizumab
Comparator (n patients)	Placebo	-
Population	Children (6 to <12 years) with uncontrolled persistent asthma	Children (6 to <12 years) with severe eosinophilic asthma
Stratification	• Eosinophilic asthma (Blood eosinophils ≥ 300 cells per microliter) • Allergic asthma (Type 2 inflammatory asthma phenotype)	• Body weight <40 kg • Body weight ≥40 kg • Eosinophilic asthma (Blood eosinophils ≥150 cells/µL at screening or ≥300 cells/µL within previous 12 months)
Primary endpoint	• Asthma exacerbations	• PK/PD
Secondary endpoints	• Pre-bronchodilator % predicted FEV1 • ACQ-7-IA • FeNO level • Time to first severe exacerbation • Time to first LOAC • Number of puffs of reliever medication • PAQLQ(S)	• Long-term safety • ACQ-7 • C-ACT • Exacerbations
Longest follow-up time	52 weeks	12 weeks (efficacy) 80 weeks (long-term safety)

Abbreviations; PK: Pharmacokinetic; PD: Pharmacodynamic; ACQ-7(-IA): Asthma Control Questionnaire 7-item (Interviewer administrated); FeNO: Nitrogenoxid; LOAC: loss of asthma control; C-ACT: Childhood Asthma Control Test; PAQLQ: Pediatric Quality of Life Questionnaire

7.2.2 Efficacy and safety – results per study

7.2.2.1 Results – LIBERTY VOYAGE

7.2.2.1.1 Efficacy results, Dupilumab

Number of severe exacerbation events

Over a 52 weeks treatment period, 212 patients with severe eosinophilic asthma were treated with dupilumab and 107 patients receiving matching placebo. The annualized rate of severe exacerbation events during the 52 week treatment period was [redacted] in the dupilumab arm [redacted] in the placebo arm resulting in a statistically significant relative risk of [redacted]) in the dupilumab-arm compared to placebo, Table 7 (24).

[redacted] of the patients in the dupilumab-arm did not experience a severe exacerbation during the 52-week treatment duration, while a small proportion of patients ([redacted] of the patients in the placebo-arm experienced no exacerbation during the same period. The difference exceeds the MCID of 10% presented in the treatment guidelines for severe asthma by the DMC(50).

Change from baseline in ppFEV1% to week 12

The predicted pre-bronchodilator ppFEV1 was measured at baseline to a mean ppFEV1 (SD±) of [redacted] in the dupilumab group [redacted] in the placebo group. In week 12, the change from baseline was estimated to [redacted] and [redacted] for the dupilumab group and placebo group. Dupilumab showed a significant LSmean difference of [redacted] compared to placebo in the Liberty Asthma VOYAGE-trial.

%-patients with >=200mL improvement in FEV1 at week 12

At week 12, a significantly higher proportion of patients in the dupilumab group had an improvement in FEV1 of 200 mL or more ([redacted] more patients) when compared to placebo.

Asthma control

Asthma control was assessed by the use of ACQ-7-AI in Liberty Asthma VOYAGE. ACQ-7-AI score were measured at baseline and at week 24. The LSmean ACQ-7-AI change from baseline in week 24 showed a change in the dupilumab group of [redacted] in the placebo group, and dupilumab showed a statistically significant improvement of [redacted] compared to placebo Table 7)

Quality of life

Quality of life was assessed using the PAQLQ-IA tool in Liberty Asthma VOYAGE. Compared to placebo, dupilumab showed a statistically significant mean improvements (indicated by higher scores on the PAQLQ-IA) in PAQLQ-IA global score over time [redacted] at week 52.

In the PRQLQ global score, dupilumab showed a significant mean improvement over time (indicated by lower score on the PRQLQ) of [redacted] at week 52 compared to placebo.

Table 17. Summary of study results Dupilumab, children with severe eosinophilic asthma, efficacy outcomes

Outcome	Dupilumab (n=212)	Placebo (n=107)	AD (95% CI)	RD (95% CI)	p-value
Efficacy results					
Annualized rate of severe asthma exacerbations during 52-week treatment period (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% Experience no exacerbation during 52-week treatment periods, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from BL at week 12 of %-ppFEV1, (±SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% patients with >=200mL improvement in FEV1 at week 12 (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from BL at week 24 of ACQ-7-IA, (±SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from BL at week 52 of PAQLQ-IA global score (+SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from BL at week 52 of PRQLQ global score (+SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD, absolute difference; BL, base line; CI, Confidence Interval; NA, not available; ppFEV1, predicted prebronchodilator FEV1; RD, relative difference. **Note:** #, p-value for RD; *, p-value for AD.

7.2.2.1.2 Safety results, Dupilumab

Please consult section 7.1.2.1.2, where safety results from the safety population in Liberty Asthma VOYAGE is described.

7.2.2.2 Results – Mepolizumab

7.2.2.2.1 Efficacy results, Mepolizumab

A total of 36 children was included in the study of mepolizumab, including 26 patients receiving 40mg mepolizumab and 10 patients receiving 100mg in part A of the study. All the pharmacokinetic parameter estimates are presented normalized to 27 kg and 50 kg (mean bodyweight for the 40 mg and 100 mg dose groups, respectively), Table 18.

Over the 12-week treatment period in part A of the study, the pharmacokinetic endpoints were found that the mepolizumab exposure ($AUC_{(0\text{-}inf)}$) to be 454.4 and 672.2 µg·day/mL for patients in the 40mg mepolizumab group and the 100 mg mepolizumab group, respectively. The C_{max} was found to be 10.2 µg/mL for patients receiving 40 mg mepolizumab and 16.3 µg/mL for patients receiving 100 mg mepolizumab. Patients who received mepolizumab 40 mg would have a $t_{½}$ of 23.6 days and a $t_{½}$ of 21.8 days for patients receiving 100 mg (18).

At baseline, respective geometric mean blood eosinophil counts were 386 and 331cells/µL in the 40 mg dose group (<40 kg) and the 100 mg dose group (≥40 kg). Blood eosinophil counts showed a marked reduction by week 12, blood eosinophil counts were reduced from baseline by 88.5% in the 40 mg dose group resulted in a reduction to 42 cells/µL and by 83.4% in the 100 mg dose group to 55 cells/µL. The results of ACQ-7 showed an improvement from baseline with a score of 1.82, to a -0.26 reduction in week 12 from baseline eligible to a ≥0.5-point reduction in 48% of the children, see Table 18 (18). The C-ACT (Childhood Asthma Control Test) score at baseline was 16.9 and showed an improvement from baseline with an increasing of 1.4 in week 12 showing an improvement in asthma control. The explanatory endpoint results are reported in **Appendix D Efficacy and safety results per study**.

7.2.2.2.2 Safety results, Mepolizumab

The long-term safety of mepolizumab was evaluated in the part B study. Results of safety will be reported based on the part B of the study. Here a total of 30 children was included to evaluate the long-term safety and pharmacodynamics of mepolizumab (51). Most children (90%) received all 13 treatments and was on treatment for average of 355 days. AEs were reported in 27 children, where the most frequent AEs reported in >10% of the patient population were bronchitis (n=9), headache (n=8), and asthma exacerbation (n=7), see Table 19. Of the 27 children experience an AE during the 52-week treatment period, 8 was experienced on-treatment and was considered related to mepolizumab (headache, upper abdominal pain, and pyrexia).

The overall incidence of SAEs were 9 patient corresponding to 30% of the total patient population. In the patient group receiving 40 mg of mepolizumab, 5 patients had a SAE, where 4 of the patients were on treatment with mepolizumab when experiencing the SAE and 1 patient had been off treatment for more than 4 weeks, Table 18. But none of these SAEs was considered treatment related. Throughout the treatment period of part B, no treatment-related changes were observed in clinical laboratory parameters or vital signs (51). Additionally, AEs are reported in **Appendix D Efficacy and safety results per study**.

Table 18. Summary of study results Mepolizumab

Outcome	Mepolizumab 40mg (n=26)	Mepolizumab 100mg (n=10)	Mepolizumab total (n=36)
Efficacy results [18]			
Pharmacokinetic (95% CI)	Normalized to 27 kg	Normalized to 50 kg	NA
$AUC_{(0\text{-}inf)}$ (µg · day/mL)	454.4 (422.1, 486.7)	675.2 (602.2, 748.2)	NA
C_{max} (µg/mL)	10.2 (9.5, 10.9)	16.3 (15.0, 17.6)	NA
$C_{max\ ss}$ (µg/mL)	17.8 (15.3, 20.2)	28.5 (25.0, 31.9)	NA

CL/F (L/day)		0.09 (0.08, 0.09)	0.15 (0.13, 0.16)	NA
C_{av} (µg/mL)		16.2 (15.1, 17.4)	24.1 (21.5, 26.7)	NA
$t_{½}$ (days)		23.6 (21.9, 25.3)	21.8 (19.6, 24.1)	NA
Pharmacodynamics				
Blood eosinophil count, cells/µL	Eosinophil count week 12, n cells/µL (95% CI)	42 (26,67)	55 (31,97)	NA
	% reduction BL at week 12	88.5%	83.4%	87.1%
ACQ-7	Change from BL at week 4	-0.55 (-1.01; -0.09)	-0.47 (-1.16, 0.21)	-0.53 (-0.89; -0.16)
	Change from BL at week 8	-0.65 (-1.15; -1.16)	-0.30(-1.19, 0.59)	-0.55 (-0.97; -0.14)
	Change from BL at week 12	-0.41 (-0.91, 0.08)	0.08 (-0.88, 1.04)	-0.26 (-0.69, 0.16)
	≥0.5 point reduction from BL, n/N (%)	11/23 (48)	5/10 (50)	16/33 (48)
C-ACT	Change from BL at week 4	1.8 (0.2, 3.5)	2.4 (-0.9, 5.7)	2.0 (0.6, 3.4)
	Change from BL at week 8	3.0 (0.7, 5.4)	1.5 (-1.6, 4.6)	2.6 (0.8, 4.4)
	Change from BL at week 12	2.1 (0.2, 4.1)	-0.3 (-4.0, 3.4)	1.4 (-0.3, 3.1)
Prebronchodilator FEV_1 (mL)	Change from BL at week 4	93 (-19, 206)	55 (-52, 162)	83 (-1, 167)
	Change from BL at week 8	90 (-17, 198)	-63 (-314, 188)	48 (-52, 148)
	Change from BL at week 12	72 (-37, 181)	2 (-175, 179)	51 (-37, 139)

Outcome	Mepolizumab 40mg (n=16)	Mepolizumab 100mg (n=10)	Mepolizumab 40/100mg (n=4)	Mepolizumab total (n=30)
Safety results [51]				
AE, n (%)	15 (94)	8 (80)	4 (100)	27 (90)
Treatment-related on-treatment AEs	4 (30)	3 (3)	1 (25)	8 (27)
AE leading to discontinuation of treatment	0	0	0	0

SAE, n (%)	5 (31)	3 (30)	1 (25)	9(30)
PD for long time safety study [51]				
Blood eosinophil count, cells/µL, geometric mean (SD log), week 52	48 (0.858)	44 (1.022)	49 (0.166)	47 (0.841)

Abbreviations: BL: Base line; $AUC_{[0\text{-}inf]}$: Area under the plasma concentration-time curve to infinity; C_{max}: Maximum plasma concentration; $t_{1/2}$: Terminal phase elimination half-life; C_{av}: average concentration; CI: confidence; interval; CL/F: apparent plasma clearance; $C_{max\ ss}$: maximum plasma concentration at steady state; PD: Pharmacodynamic; FEV1: Forced expiratory volume in second 1
Note: Data are normalized to 27 kg (mean in the <40 kg group receiving 40 mg mepolizumab s.c.), 50 kg (mean in the ≥40 kg group receiving 100 mg mepolizumab s.c.).

Table 19. Most frequent AEs (>10% of total population) reported in the Mepolizumab study

Most frequent AEs, n (%)	Mepolizumab 40mg (n=16)	Mepolizumab 100mg (n=10)	Mepolizumab 40/100mg (n=4)	Mepolizumab total (n=30)
Bronchitis	5 (31)	3 (30)	1 (25)	9 (30)
Headache	4 (25)	3 (30)	1 (25)	8 (27)
Asthma	4 (25)	2 (20)	1 (25)	7 (23)
Nasopharyngitis	3 (19)	1 (10)	2 (50)	6 (20)
Upper respiratory tract infection	2 (13)	2 (20)	1 (25)	5 (17)
Influenza	3 (19)	0	1 (25)	4 (13)

Abbreviations: AE: Adverse events
Note: Mepolizumab 40/100mg covers patients in part A that changed from receiving mepolizumab 40 mg to receiving 100 mg during to weight gain.

7.2.3 Comparative analyses

Due to the heterogeneity between the two studies, as well as poor data for mepolizumab, a narrative comparison has been conducted on the outcomes where possible.

7.2.3.1 Number of exacerbations

Exacerbation rates were not explored in the mepolizumab trial, therefore narrative comparison will not be possible for this comparison. Results from Liberty Asthma VOYAGE is instead summarised below.

Results from Liberty Asthma VOYAGE indicate that dupilumab significantly reduces the risk of severe exacerbations compared to placebo in patient with severe eosinophilic asthma. A significantly higher proportion of patient in the dupilumab group did not experience an exacerbation during the 52-week follow-up period compared to placebo in the trial [redacted] This difference exceeded the MCID of 10% stated in the treatment guidelines for severe asthma by the DMC(50).

It was not possible to determine relative efficacy of dupilumab compared to mepolizumab in terms of reducing severe exacerbation, as no data is available for the comparator mepolizumab in children with severe eosinophilic asthma.

For the health economic analysis, the relative effect is assumed to be equal to the one observed in adults/adolescents. Please refer to section 8.2.2.4.1 for information on the analysis.

Table 20. Summary of exacerbation-related outcomes in Liberty Asthma VOYAGE

Study/outcome	Intervention arm	Comparator arm	AD (95% CI)	RD (95% CI)	p-value
Liberty Asthma VOYAGE	**Dupilumab (n=212)**	**Placebo (n=107)**			
Annualized rate of severe asthma exacerbations during 52-week treatment period (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% Experience no exacerbation during 52-week treatment periods, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD, absolute difference; CI, Confidence Interval; NA, not available; ppFEV1, predicted prebronchodilator FEV1; RD, relative difference. **Note:** #, p-value for RD; *, p-value for AD.

7.2.3.2 Change from baseline in ppFEV1% to week 12

The Liberty Asthma VOYAGE-trial demonstrated dupilumab's ability to improve the lung function in terms of change in FEV% of patients and induced a significantly larger change compared to placebo.

For mepolizumab, there was no clear pattern of change in terms of change in mean pre-bronchodilator FEV1 compared to baseline at 12 weeks.

It appears that dupilumab will have a more profound impact on the change in FEV1 in patients when compared to mepolizumab. However, due to the nature of the narrative comparison, it is not possible to come to a definitive conclusion on whether dupilumab is a superior treatment compared to mepolizumab in terms of improvement in lung function.

Table 21. Summary of ppFEV1% results in Liberty Asthma VOYAGE, severe eosinophilic asthma subgroup

Outcome	Dupilumab (n=212)	Placebo (n=107)	AD (95% CI)	RD (95% CI)	p-value
Change from BL at week 12 of %-ppFEV1, (±SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 22. Summary of FEV1 results in mepolizumab children-trial(4)

Outcome		Mepolizumab 40mg (n=26)	Mepolizumab 100mg (n=10)	Mepolizumab total (n=36)
Prebronchodilator FEV_1 (mL)	Change from BL at week 4	93 (-19, 206)	55 (-52, 162)	83 (-1, 167)
	Change from BL at week 8	90 (-17, 198)	-63 (-314, 188)	48 (-52, 148)
	Change from BL at week 12	72 (-37, 181)	2 (-175, 179)	51 (-37, 139)

7.2.3.3 %-patients with >=200mL improvement in FEV1 at week 12

This endpoint has only been reported for dupilumab in the Liberty Asthma VOYAGE-trial, please see section 7.2.2.1.1. No data is available for mepolizumab on this endpoint.

7.2.3.4 Asthma control

Asthma control was measured in both trials using ACQ-7, at 24 weeks and 12 weeks respectively, however, the mepolizumab-trial did not include a control arm in the study design, complicating the narrative comparison for this endpoint. In Liberty Asthma VOYAGE, the patients in dupilumab arm had a mean change from baseline at week 24 of [redacted], while the total patient population in the mepolizumab achieved a change from baseline at week 12 of [redacted]. Dupilumab demonstrated a larger numerical from baseline compared mepolizumab in terms of asthma control measured using ACQ-7. However, due to the heterogeneity between the trial in study design, it is not possible to draw a conclusion on whether dupilumab is statistically superior to mepolizumab in terms of asthma control.

Table 23. Summary of ACQ-7 results in Liberty Asthma VOYAGE, severe eosinophilic asthma subgroup

Study/outcome	Intervention arm	Comparator arm	AD (95% CI)	RD (95% CI)	p-value
Liberty Asthma VOYAGE	**Dupilumab (n=271)**	**Placebo (n=134)**			
Change from BL at week 24 of ACQ-7-IA, (±SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 24. Summary of ACQ-7 results in mepolizumab children-trial(18)

Outcome		Mepolizumab 40mg (n=26)	Mepolizumab 100mg (n=10)	Mepolizumab total (n=36)
ACQ-7	Change from BL at week 4	-0.55 (-1.01; -0.09)	-0.47 (-1.16, 0.21)	-0.53 (-0.89; -0.16)

Change from BL at week 8	-0.65 (-1.15; -1.16)	-0.30(-1.19, 0.59)	-0.55 (-0.97; -0.14)
Change from BL at week 12	-0.41 (-0.91, 0.08)	0.08 (-0.88, 1.04)	-0.26 (-0.69, 0.16)
≥0.5 point reduction from BL, n/N (%)	11/23 (48)	5/10 (50)	16/33 (48)

7.2.3.5 Quality of life

This endpoint has only been reported for dupilumab in the Liberty Asthma VOYAGE-trial, please see section 7.2.2.1.1. No data is available for mepolizumab on this endpoint.

7.2.3.6 Safety outcome

Proportion of patients with serious adverse events

As it was not possible to perform statistical indirect comparison, due to the heterogenic nature of the two studies, a narrative comparison between the two studies will be conducted instead. In Liberty Asthma VOYAGE, the risk of having an SAE were similar between the dupilumab arm and the placebo group. In the mepolizumab-trials, long-term safety follow-up, 30% of the patients experienced a SAE during the 80-week follow-up period. Based on a narrative comparison between the two trials, it appears that dupilumab is associated with a numerical smaller risk of SAEs compared to mepolizumab, although differences in follow-up time, study design and patient populations, makes the comparison uncertain. The results of this narrative comparison should therefore be interpreted with caution.

Table 25. Summary of proportion with serious adverse events – Liberty Asthma VOYAGE vs. mepolizumab children-trial(51)

Study/outcome	Intervention arm	Comparator arm	AD (95% CI)	RD (95% CI)	p-value
Liberty Asthma VOYAGE	**Dupilumab (n=271)**	**Placebo (n=134)**			
SAE, n (%)	13 (4.8)	6 (4.5)	0.32% (-4.01% - 4.65%)	1.07 (0.42 - 2.76)	0.8937* 0.8950#
Mepolizumab-trial	**Mepolizumab (n=30)**	**NA**			
SAE, n (%)	9 (30)	NA	NA	NA	NA

Abbreviations: AD, absolute difference; CI, Confidence Interval; SAE, Severe adverse events. **Note**: #, p-value for RD; *, p-value for AD.

Proportion of patients discontinued due to adverse events

No discontinuation related to AEs were reported in the mepolizumab study, while 5 patients discontinued dupilumab treatment in Liberty Asthma VOYAGE, although the dupilumab group did not significantly differ from the placebo group in terms of discontinuations. No difference between dupilumab and mepolizumab could be quantified, due to the lack of common comparator arm in the trials, and the heterogeneity between the two trials.

Table 26. Summary of proportion of patients discontinued due to adverse events – Liberty Asthma VOYAGE vs. mepolizumab children-trial(51)

Outcome	Intervention arm	Comparator arm	AD (95% CI)	RD (95% CI)	p-value
Liberty Asthma VOYAGE	**Dupilumab (n=271)**	**Placebo (n=134)**			
AEs leading to discontinuation, n (%)	5 (1.8)	2 (1.5)	0.35% (-2.25% - 2.96%)	1.24 (0.24 - 6.29)	0.8029* 0.8103#
Mepolizumab-trial	**Mepolizumab (n=30)**	**NA**			
AEs leading to discontinuation, n (%)	0 (0)	NA	NA	NA	NA

Abbreviations: AE, Adverse event; AD, absolute difference; CI, Confidence Interval; SAE, Severe adverse events. **Note**: #, p-value for RD; *, p-value for AD.

7.3 Efficacy and safety of dupilumab compared to placebo for treatment of severe asthma characterized by elevated FeNO levels in children aged 6 to <12

7.3.1 Relevant studies

Only one study was found relevant to assess the efficacy and safety of dupilumab compared to placebo in children aged 6 to <12 with severe asthma with elevated FeNO, as a randomized direct head-to-head study has been conducted.

7.3.1.1 Liberty Asthma VOYAGE

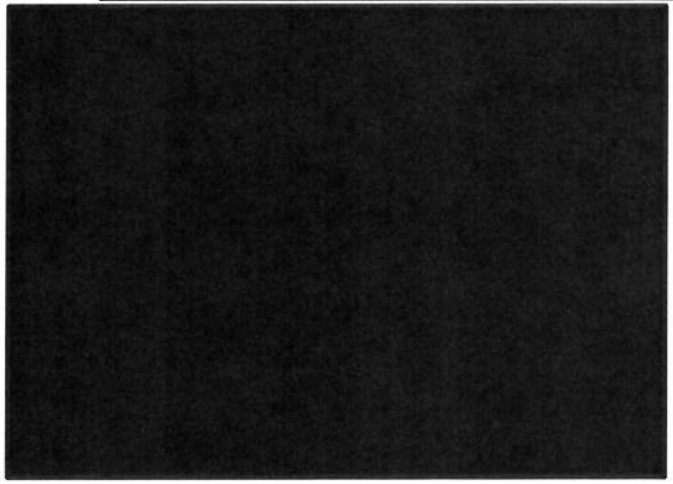
The description of the Liberty Asthma VOYAGE study can be found in section 7.1.1.1 (24). For the population with severe asthma with elevated FeNO expression, the Liberty Asthma VOYAGE study was the only relevant study to illuminate the safety and efficacy of dupilumab in treatment of these patients. Currently no treatment is available for this population.

However, as Liberty Asthma VOYAGE trial had broad eligibility criteria, and patients were not selected for enrolment based on phenotypic traits. In order to cover this patient population, a subgroup analysis have been conducted using data from the Liberty Asthma VOYAGE trial, defined as:

- **Severe asthma with elevated FeNO**: Data is not sufficient to create a valid subgroup analysis for a subpopulation with elevated FeNO patients without concomitant eosinophilia and without concomitant allergy. Therefore, available data for patients with elevated baseline FeNO (≥20 ppb) regardless of EOS and allergy status is provided instead. Based on Danish Experts, there is a high unmet need for improved treatment outcomes for this small group of patients. Currently, they have no escalation treatment options.

Asthma is a heterogeneous disease, and most patients are characterised by having more than 1 of several phenotypic traits. Hence, patients with eosinophilic asthma are often also allergic and vice versa. This has been confirmed in a recent real-world practice study, including patients from Europe (52). Similarly, patients with elevated FeNO will often possess phenotypic traits of eosinophilic and/or allergic asthma as well. This has also recently been confirmed in another real-world study, including patients from Sweden (53). As the sample size for an elevated FeNO subgroup without any allergies or eosinophilia were very limited, and since there is also a significant overlap between the eosinophilic and allergic patient populations defined by current Danish treatment guidelines, as observed in Liberty Asthma VOYAGE, see Figure 8for this subgroup, we have provided available data for patients with elevated baseline FeNO (≥20 ppb) regardless of EOS and allergy status. Data for the subgroup with non-allergic asthma with high EOS and FeNO are presented in Appendix D Efficacy and safety results per study.

Figure 8. [redacted]



7.3.2 Efficacy and safety – results per study

Only results from the subgroup analysis based on Liberty Asthma VOYAGE will be reported for the patient population with severe asthma with elevated FeNO.

7.3.2.1 Efficacy results – Liberty Asthma VOYAGE

Number of severe exacerbation events

Over a 52 weeks treatment period, 254 patients with severe asthma with elevated FeNO were treated with dupilumab and 130 patients receiving placebo. The annualized rate of severe exacerbation events during the 52 week treatment period was 0.286 in the dupilumab arm and 0.598 in the placebo arm resulting in a statistically significant relative risk of 0.484 (0.330 – 0.709, p<0.001) in the dupilumab-arm compared to placebo, Table 27 (24).

[redacted] of the patients in the dupilumab-arm did not experience a severe exacerbation during the 52-week treatment duration, while a smaller proportion of patients [redacted] of the patients in the placebo-arm experienced no exacerbation during the same period. Resulting in a statistically significant absolute difference of [redacted] in favour of dupilumab, which exceeds the MCID of 10% presented by the DMC in the treatment guidelines for severe asthma(50).

Change from baseline in ppFEV1% to week 12

The predicted pre-bronchodilator ppFEV1 was measured at baseline to a mean ppFEV1 (SD±) of [redacted] in the dupilumab group and [redacted] in the placebo group. In week 12, the change from baseline was estimated [redacted] and [redacted] for the dupilumab group and placebo group. Dupilumab showed a significant LSmean difference of [redacted] compared to placebo in the Liberty Asthma VOYAGE-trial for the subgroup with severe asthma with elevated FeNO.

%-patients with ≥200mL improvement in FEV1 at week 12

At week 12, a significantly higher proportion of patients in the dupilumab group had an improvement in FEV1 of 200 mL or more [redacted] when compared to placebo.

Asthma control

Asthma control were assessed by the use of ACQ-7-AI in Liberty Asthma VOYAGE. ACQ-7-AI score were measured at baseline and at week 24. The LSmean ACQ-7-AI change from baseline in week 24 showed a change in the dupilumab group of [redacted] in the placebo group, and dupilumab showed a significant improvement of [redacted] compared to placebo [redacted].

Quality of life

Quality of life was assessed using the PAQLQ-IA tool in Liberty Asthma VOYAGE. Dupilumab showed a statistically significant mean improvements (indicated by higher scores on the PAQLQ-IA) in PAQLQ-IA global score over time of [redacted] at week 52 compared to placebo.

In the PRQLQ global score, dupilumab showed a significant mean improvement over time (indicated by lower score on the PRQLQ) of [redacted] at week 52 compared to placebo.

Table 27. Summary of study results Dupilumab, children with severe asthma with elevated FeNO, efficacy outcomes

Outcome	Dupilumab (n=254)	Placebo (n=130)	AD (95% CI)	RD (95% CI)	p-value
Efficacy results					
Annualized rate of severe asthma exacerbations during 52-week treatment period (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% Experience no exacerbation during 52-week treatment periods, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from BL at week 12 of ppFEV1, (±SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% patients with >=200mL improvement in FEV1 at week 12 (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from BL at week 24 of ACQ-7-IA, (±SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from BL at week 52 of PAQLQ-IA global score (+SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from BL at week 52 of PRQLQ global score (+SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD, absolute difference; BL, base line; CI, Confidence Interval; NA, not available; ppFEV1, predicted prebronchodilator FEV1; RD, relative difference. **Note:** #, p-value for RD; *, p-value for AD.

7.3.2.1.1 Safety results, Dupilumab

Please consult section 7.1.2.1.2, where safety results from the safety population in Liberty Voyage is described.

7.3.3 Comparative analyses

No comparative analysis has been conducted as the study presented is a direct head-to-head study and consequently leaves a comparative analysis redundant.

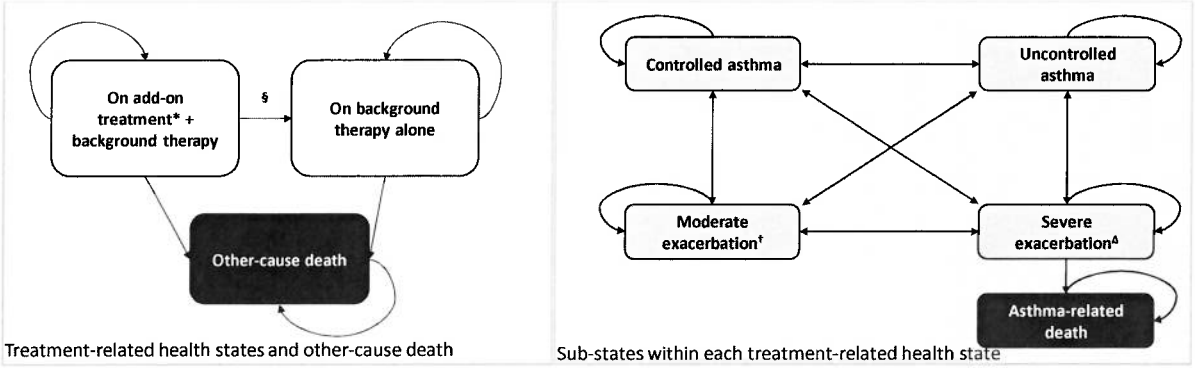
8. Health economic analysis

8.1 Model

8.1.1 Model structure

A Markov cohort model was developed in Microsoft excel to reflect both the chronic day-to-day asthma symptoms that patients with uncontrolled persistent asthma experience, which would influence their QoL, as well as the risk these patients may also experience intermittent asthma exacerbations that can vary in severity and in some instances, lead to death. The model structure was developed based on a previous health economic model for adults and adolescents, which was accepted by NICE(25) for severe persistent asthma and suggestions by clinicians to make sure that the structure of the model was consistent with clinical practice. A three-health state containing the health states "On add-on treatment + background treatment", "On background treatment alone", and "Other cause death" that in the two treatment-related health states contains a five-sub-state model. The transition from the "On add-on treatment + background therapy" to the "On background therapy only health states are modelled as a function of: 1) long-term continuation rules and other reasons for discontinuation. It is possible to model this as a function of response as well. Patients enter the model in an "uncontrolled asthma" health state, and transition between the "controlled asthma", "moderate exacerbation" and "severe exacerbation" health states according to transition probabilities calculated from clinical trial data. From the severe exacerbation health state, patients can transition to the fifth health state in the five-sub-state model was asthma-related death, which is an absorbing state, see Figure 9.

Figure 9. Structure of the model used in the economic analysis



In the five-sub-state model, two states representing a situation where patients experience day-to-day symptoms of asthma at varying levels (thereby influencing QoL) but without a significant worsening of symptoms (i.e., none of the types of asthma exacerbations defined further below):

- **'Uncontrolled asthma' state**
- **'Controlled asthma' state**

Two states relating to the occurrence of significant worsening of symptoms, with two levels of severity of asthma exacerbations:

- **'Moderate exacerbation' state**
- **'Severe exacerbation' state**

Moderate exacerbations are defined based on the loss of asthma control (LOAC) events (excluding severe exacerbation events) as collected in the QUEST trial(54) or the VOYAGE trial.(55) As such, at least one of the following criteria must be satisfied to count as a moderate exacerbation:

- ≥ 6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24-hour period (compared with baseline) on two consecutive days
- ≥ 20% decrease in pre-bronchodilator FEV_1 compared with baseline [*only applies for definition of LOAC events in the QUEST trial*]
- Increase in ICS dose ≥ 4 times than the dose at Visit 2
- A decrease in AM or PM peak flow of 30% or more on two consecutive days of treatment, based on the defined stability limit. The treatment period stability limit is defined as the respective mean AM or PM peak expiratory flow (PEF) obtained over the last seven days prior to randomisation (Day 1)

Severe exacerbations are defined based on the severe exacerbation events as collected in the dupilumab trials. As such, at least one of the following criteria must be satisfied to count as a severe exacerbation:

- Use of systemic corticosteroids for ≥ 3 days
- Hospitalisation or emergency room visit because of asthma, requiring systemic corticosteroids

One state representing an absorbing state were patients no longer can transition between the health states:

- **'Asthma-related death' state**

After discontinuation, patients cannot revert to receiving add-on treatment. Once patients discontinue add-on treatment, no residual treatment effect is assumed. Rather, patients discontinuing add-on treatment are assumed to have equivalent risks of transitioning between health states to patients treated with background therapy only, regardless of the reason for discontinuation.

8.1.1.1 Transition probabilities

Progression of patients through the live health states is implemented in the model by using a set of transition probabilities between these different health states. Patients are assigned a certain probability to remain in the same state at the next cycle (subject to surviving), and three (five-sub-state model) separate probabilities of moving to each of the other states in the next cycle, as illustrated in Table 28, Table 29 and Table 30. For dupilumab and for background therapy, the transition probabilities are informed by patient-level data from the dupilumab trial (VOYAGE). Estimation of transition probabilities involved counting the number of patients in each health state every four weeks (consistent with the cycle length), along with the frequency of transitions to other health states from that health state.

Table 28. Adjusted transition probabilities for severe allergic asthma, while using data from trials conducted in children, VOYAGE data

From\To	Controlled Asthma	Uncontrolled Asthma	Moderate Exacerbation	Severe Exacerbation	Controlled Asthma	Uncontrolled Asthma	Moderate Exacerbation	Severe Exacerbation	Controlled Asthma	Uncontrolled Asthma	Moderate Exacerbation	Severe Exacerbation
	0–12 Weeks				12–52 Weeks				52+ weeks			
Background therapy (200 mg Q2W)												
Controlled Asthma	[redacted]											
Uncontrolled Asthma	[redacted]											
Moderate Exacerbation	[redacted]											
Severe Exacerbation	[redacted]											
Dupilumab + Background therapy (200 mg Q2W)												
Controlled Asthma	[redacted]											
Uncontrolled Asthma	[redacted]											
Moderate Exacerbation	[redacted]											
Severe Exacerbation	[redacted]											

Note: Adjusted transition probabilities, with risk of experiencing exacerbations dependent on current health state, but not on time since treatment initiation; and using observed data with exceptions.

Table 29. Adjusted transition probabilities for severe eosinophilic asthma, while using data from trials conducted in children, VOYAGE data

From\To	Controlled Asthma	Uncontrolled Asthma	Moderate Exacerbation	Severe Exacerbation	Controlled Asthma	Uncontrolled Asthma	Moderate Exacerbation	Severe Exacerbation	Controlled Asthma	Uncontrolled Asthma	Moderate Exacerbation	Severe Exacerbation
	0–12 Weeks				12–52 Weeks				52+ weeks			
Background therapy (200 mg Q2W)												
Controlled Asthma	[redacted]											
Uncontrolled Asthma	[redacted]											
Moderate Exacerbation	[redacted]											
Severe Exacerbation	[redacted]											
Dupilumab + Background therapy (200 mg Q2W)												

Controlled Asthma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled Asthma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: Adjusted transition probabilities, with risk of experiencing exacerbations dependent on current health state, but not on time since treatment initiation; and using observed data with exceptions.

Table 30. Adjusted tTransition probabilities for severe asthma with high FeNO, while using data from trials conducted in children, VOYAGE data

From\To	Controlled Asthma	Uncontrolled Asthma	Moderate Exacerbation	Severe Exacerbation	Controlled Asthma	Uncontrolled Asthma	Moderate Exacerbation	Severe Exacerbation	Controlled Asthma	Uncontrolled Asthma	Moderate Exacerbation	Severe Exacerbation
	0–12 Weeks				12–52 Weeks				52+ weeks			
Background therapy (200 mg Q2W)												
Controlled Asthma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled Asthma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab + Background therapy (200 mg Q2W)												
Controlled Asthma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled Asthma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: Adjusted transition probabilities, with risk of experiencing exacerbations dependent on current health state, but not on time since treatment initiation; and using observed data with exceptions.

8.1.2 Patient population

See section 5.1.1 for patient populations relevant for this submission.

8.1.3 Perspective, Time horizon, and Cycle length

Perspective

The model considers a Danish restrictive societal perspective, consistent with the guidelines presented by the DMC (56).

Time horizon

A lifetime horizon was considered most appropriate to capture the full benefits associated with the treatment, as treatment of uncontrolled persistent asthma is anticipated to continue over the whole life of the patient once diagnosed and is in line with time horizons used in previous HTA submission for dupilumab (14).

Cycle length

A four-week cycle length was used in the model as this length correspond to the duration of the treatment cycle for mepolizumab and the frequency of exacerbation reported in the dupilumab trial (24, 57).

8.1.4 Discounting

A discount rate of 3.5% until year 35 and 2.5% beyond year 35 was applied to costs, as defined by the Danish Ministry of Finance and in the DMC guidelines (56).

8.1.5 Half-Cycle Correction

When accumulating costs and utilities, a half-cycle correction (HCC) is applied to correct for discrete time. This correction assumes that transitions occur halfway through a cycle and corrects for state-membership being known in the beginning and end of the cycle but not in between. Due to the short cycle length of four weeks, the half-cycle correction was not expected to have a large impact on the results, but it was included in the model for completeness.

8.1.6 Model Outcomes

The analysis calculates benefit in terms of life years (LYs) and quality-adjusted life years (QALYs). Base case results were generated using QALYs as the measure of benefit and the primary outcome was incremental cost per QALY. A list of model outcomes reported for the base case in the model are reported in Table 31. Graphical representation of the sensitivity results in the form of a tornado diagram for deterministic sensitivity analysis (DSA) and cost-effectiveness acceptability curve (CEAC) for probabilistic sensitivity analysis (PSA) are also included.

Table 31. Model outputs

Cost Outcomes	Health Outcomes	Incremental and Cost-effectiveness Outcomes
• Overall costs disaggregated by each cost category within the model: o Drug acquisition o Add-on treatment o Background therapy o Drug administration o Monitoring o Transportation and patients/relatives o Disease management o Exacerbation-related	• Total LYs • Total QALYs • Number of exacerbations avoided o Number of moderate exacerbations o Number of severe exacerbations o Requiring office visit o Requiring ED visit o Requiring hospitalization • Total number of deaths o Number of exacerbation-related deaths avoided o Number of non-asthma deaths • Total LYs o In controlled asthma health state o In uncontrolled asthma health state • In moderate exacerbation health state • In severe exacerbation health state	• Incremental costs • Incremental LYs • Incremental QALYs • Incremental cost per life year gained • Incremental cost per QALY gained • Incremental cost per exacerbation avoided • Number of exacerbations avoided • Number of moderate exacerbations avoided • Number of severe exacerbations avoided o Requiring office visit o Requiring ED visit o Requiring hospitalization • Number of exacerbation-related deaths avoided • Number of moderate exacerbations

*Number of needed to treat

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1 Presentation of input data used in the model and how they were obtained

A summary of input data is presented in Table 32. The model was based on efficacy and safety data from the clinical trial LIBERTY VOYAGE for the child population and QUEST for adult population, Omalizumab (IA05), and mepolizumab trial as presented in section 7.1.1.1, 7.1.1.2, and 7.2.1.2. An exploratory Bucher's ITC was used to compare dupilumab versus omalizumab and dupilumab versus mepolizumab, derived from Liberty Asthma VOYAGE, IA05, and the mepolizumab study. Details on health state utility values (HSUV) are present in section 8.4. AEs were not included in the model, however, the safety profile of dupilumab, omalizumab, and mepolizumab can be found in section 7.1.2.1.2, 7.1.2.2.2, and 7.2.2.2.2.

Table 32. Input data used in the model [sources should be cited where available]:

Name of estimates*	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	How is the input value obtained/estimated**
Severe exacerbation rates	See section 8.2.2.4.2	Input values from VOYAGE (QUEST for adult/adolescent) for Dupilumab and SOC arms. Vs Omalizumab: Bucher ITC on Liberty asthma VOYAGE vs AI05 for children; Bucher ITC on Liberty asthma DRI, QUEST vs EXTRA, INNOVATE for adult/adolescent (Bateman 2020). Vs mepolizumab: Bucher ITC on Liberty asthma DRI, QUEST vs DREAM, MENSA, MUSCA for adult/adolescent (Bateman 2020).
Uncontrolled Asthma	See section 8.2.2.4.3	Exploratory analysis
Utilities	See section 8.4	EQ-5D-Y3L Liberty Asthma VOYAGE for child period, EQ-5D-5L Liberty Asthma QUEST for adult/adolescent period
Transition probability	See section 8.1.1.1	Transition probability matrix
Costs	See section 8.5	DRG, Medicinpriser.dk, Medicinrådet - "Værdisætning af enhedsomkostninger", krl.dk
Adverse events	See section 7.1.2.1.2, 7.1.2.2.2, and 7.2.2.2.2	Not included in the model

* Some of these estimates will be presented in other tables in the document. This table is a summary.

** Calculations: [If intermediate outcome measures were linked to final outcomes, describe them here (for example, if a change in a surrogate outcome was linked to a final clinical outcome). Explain how the relationship was estimated, what sources of evidence were used, how the sources of evidence were identified (e.g. systematic literature review) and what other evidence exists. Details must be provided in a separate appendix with reference here.]

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

The three subpopulations described in section 5.1.1 are included in this economic assessment. Please see section 7.3.1.1 for the further description of the subgroup analyses and differentiation of the elevated FeNO level subgroup.

The baseline characteristics of patients in the Liberty Asthma VOYAGE, IA05, and mepolizumab trials can be found in section 5.1.1 and Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety.

8.2.2.2 Intervention

Dupilumab is an s.c. administrated therapy of 200 mg solution Q2W or 300 mg solution Q4W. The efficacy of dupilumab 300 mg every 4 weeks (Q4W) in children aged 6 to 11 years with a body weight < 60 kg is extrapolated from the efficacy of 100mg and 200 mg Q2W in VOYAGE and 200 mg and 300 mg Q2W in adults and adolescents (QUEST). Patients who completed the treatment period of the VOYAGE study could participate in the open label extension study (EXCURSION). Eighteen patients (≥ 15 kg to < 30 kg) out of 365 patients were exposed to 300 mg Q4W in this study, and the safety profile was similar to that seen in VOYAGE.

The 300mg Q4W dosing regimen minimizes the frequency of injections and simplifies the dosing schedule, which is an advantage as physicians/caregivers/patients currently treat children. The 300mg Q4W dosing regimen is used for children with atopic dermatitis and a body weight from 15 mg to less than 60 kg with 300 mg Q4W and are familiar with that procedure. Additionally, the Q4W dosing regime is aligned with other treatment options for pediatric asthma and thus is familiar to physicians and could support patients/caregivers.

Currently dupilumab is recommended as 1st choice for adults with severe allergic asthma and as 4th choice for adult patients with severe eosinophilic asthma (19). Dupilumab have been given positive opinion by EMA for treatment of children within the three subtypes of asthma. It is expected that dupilumab will be administered at the hospital in the child population.

Table 33. Description of dupilumab as used in the model

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	The recommended dose of dupilumab for paediatric patients aged 6 to 11 years is according to body weight are either: • Body weight ≤60 kg with a dosage of 300 mg every 4 weeks (Q4W), administered as a subcutaneous injection	Dupilumab is an s.c. administrated therapy of 300 mg Q4W (body weight <60 kg) | 200 mg Q2W (body weight ≥60 kg)	Dupilumab is an s.c. administrated therapy of 300 mg Q4W (body weight <60 kg) | 200 mg Q2W (body weight ≥60 kg)

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
	• Body weight >60 kg with a dosage of 200 mg every 2 weeks (Q2W), administered as a subcutaneous injection Or • Body weight >30 kg with a dosage of 200 mg dupilumab every 2 weeks (Q2W), administered as a subcutaneous injection • Body weight ≤30 kg with a dosage of 100 mg dupilumab Q2W, administered as a subcutaneous injection		
Length of treatment (time on treatment) (mean/median)	Consider end of treatment if unacceptable toxicity, if asthma remains uncontrolled or worsens during treatment.	Consider end of treatment if unacceptable toxicity, if asthma remains uncontrolled or worsens during treatment.	Consider end of treatment if unacceptable toxicity, if asthma remains uncontrolled or worsens during treatment.
The pharmaceutical's position in Danish clinical practice	Currently used as treatment for adult patients with severe allergic asthma and severe eosinophilic asthma respectively	Treatment for patients aged 6 to ≥11 years diagnosed with severe allergic -, severe eosinophilic - and severe elevated FeNO level asthma	Treatment for patients aged 6 to ≥11 years diagnosed with severe allergic -, severe eosinophilic - and severe elevated FeNO level asthma

8.2.2.3 Comparators

As discussed in section 5.2, different treatments are currently used in Denmark to treat patients in the different subpopulations. The comparators used in this economic assessment is omalizumab and mepolizumab for patients with severe allergic asthma and severe eosinophilic asthma respectively. For the last population of patients with elevated FeNO expression, SoC was selected as the comparator as no treatments has been recommended for this population. These treatments are used in the model and alignment with the treatment recommendation from the DMC (19).

Table 34. Comparator

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Omalizumab			

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Posology	The appropriate dose and frequency of omalizumab is determined by baseline IgE (IU/ml), measured before the start of treatment, and body weight (kg). Prior to administration of the initial dose, patients should have their IgE level determined by any commercial serum total IgE assay for their dose assignment. Based on these measurements, 75 to 600 mg of omalizumab in 1 to 4 injections may be needed for each administration. The maximum recommended dose is 600 mg omalizumab every two weeks.	Weight and IgE based, dosing done to dosing scheme in Figure 21, varies from 75 to 600 mg of omalizumab in 1 to 4 injections	The appropriate dose and frequency of omalizumab is determined by baseline IgE (IU/ml), measured before the start of treatment, and body weight (kg). Prior to administration of the initial dose, patients should have their IgE level determined by any commercial serum total IgE assay for their dose assignment. Based on these measurements, 75 to 600 mg of omalizumab in 1 to 4 injections may be needed for each administration. The maximum recommended dose is 600 mg omalizumab every two weeks.
Length of treatment	Omalizumab is intended for long-term treatment. Consider end of treatment if unacceptable toxicity, if asthma remains uncontrolled or worsens during treatment.	Omalizumab is intended for long-term treatment. Consider end of treatment if unacceptable toxicity, if asthma remains uncontrolled or worsens during treatment.	Omalizumab is intended for long-term treatment. Consider end of treatment if unacceptable toxicity, if asthma remains uncontrolled or worsens during treatment.
The comparator's position in the Danish clinical practice	Used in 1L for children with severe allergic asthma and 2L for adult patients with severe allergic asthma.	Used in 1L for children with severe allergic asthma and 2L for adult patients with severe allergic asthma.	
Mepolizumab			
Posology	The recommended dose of mepolizumab is 40 mg or 100 mg administered subcutaneously once every 4 weeks.	The recommended dose of mepolizumab is 40 mg for children (aged 6 to <12), or 100 mg for adults administered subcutaneously once every 4 weeks.	The recommended dose of mepolizumab is 40 mg or 100 mg administered subcutaneously once every 4 weeks.
Length of treatment	Mepolizumab is intended for long-term treatment. Consider end of treatment if unacceptable toxicity, if asthma remains uncontrolled or worsens during treatment	Mepolizumab is intended for long-term treatment. Consider end of treatment if unacceptable toxicity, if asthma remains uncontrolled or worsens during treatment	Mepolizumab is intended for long-term treatment. Consider end of treatment if unacceptable toxicity, if asthma remains uncontrolled or worsens during treatment

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
The comparator's position in the Danish clinical practice	Used in 1L for both adults and children with severe eosinophilic asthma	Used in 1L for both adults and children with severe eosinophilic asthma	

8.2.2.4 Relative efficacy outcomes

8.2.2.4.1 Dupilumab versus omalizumab

The clinical efficacy of dupilumab versus omalizumab was incorporated in the model based on the results of an indirect treatment comparison (ITC) of annualized severe exacerbation rates. Comparisons to mepolizumab were not feasible given significant differences in the study designs, patient characteristics and outcomes compared to the VOYAGE trial.

Table 35. Populations for biologics as per Label Examined in the Indirect Treatment Comparisons

Treatment	ICS	EOS at Baseline	Severe Exacerbations in Previous Year	Age	Other
Child Patients					
Mepolizumab	Medium/high dose	≥ 150	≥ 2	≥6-<12	NA
Omalizumab	Medium/high dose	≥ 150	≥ 1	≥6-<12	IgE 30≥ IU/mL

The ITC comparing dupilumab versus omalizumab included two trials; Liberty Asthma VOYAGE and IA05. These trials also varied with regards to study design, patient populations, and the definition of severe exacerbations, and as such a series of exploratory analyses were performed, including data from the type 2 populations from both trials and an 'omalizumab-like type 2' subgroup from VOYAGE.

The 'omalizumab-eligible' subgroup attempted to better align patients from VOYAGE with those in the IA05 trial, based on an allergic phenotype and corresponding to the inclusion criteria of IA05, which was defined by:

- Baseline weight between 20-150 kg and serum IgE level of 30 to 1300 IU/mL and weight-IgE values combinations based on omalizumab dosing table
- At least 1 positive perennial allergen-specific IgE (concentration ≥0.35 IU/mL) or at least 1 positive seasonal allergen-specific IgE (concentration ≥0.35 IU/mL)

It should be noted that the allergic phenotype in IA05 was based on skin prick test or a positive in vitro response to ≥1 perennial allergen. These tests were not performed as part of the VOYAGE trial, and therefore the presence of 1 positive perennial or seasonal allergen specific IgE was used as a proxy for the allergic phenotype in IA05.

To account for differences in definitions of severe exacerbations and baseline risk observed (i.e., rates in the placebo arms) between the VOYAGE and IA05 trials, a new definition was derived via post hoc analyses of VOYAGE. This definition was derived to better align with the definition in IA05 which was defined as worsening of asthma symptoms requiring systemic corticosteroids for ≥3 days or doubling of baseline ICS dose. The definition of severe exacerbations in VOYAGE was asthma requiring systemic corticosteroids for ≥3 days or hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids. The new definition of exacerbations from VOYAGE was defined as 'deterioration of asthma' and was defined as asthma requiring systemic corticosteroids for ≥3 days or increased ICS dose ≥4 times at Visit 2. The modified definition was validated by clinical experts as being more comparable to the definition of clinically significant exacerbations used in study IA05, with the caveat that doubling of ICS was not available from VOYAGE, as permitted in IA05.

Analyses were based on the annualized rates from both trials, however, the annualized rate at 24-weeks was used from IA05 since after 24-weeks the trial included an ICS dose reduction phase.

Results from the exploratory Bucher ITCs based on VOYAGE and IA05 are presented in Table 36. Dupilumab had a numerical advantage over omalizumab for improvements severe exacerbations based on both definitions from VOYAGE and in both omalizumab-like type 2 and type 2 populations. For the base case, the severe exacerbation estimate is used within the model.

Table 36. Results of exploratory Bucher

Definition of Severe Exacerbation	Rate Ratio (95% CI)	
	Type 2	**Omalizumab-like type 2**
Severe Exacerbation	[redacted]	[redacted]
Asthma Deterioration	[redacted]	[redacted]

To derive transition probabilities for omalizumab, the RR was converted to a rate using -ln (1-transition probability) (58). The RR was applied to the rate for dupilumab (all patients) and converted back to a probability using 1-exp(-rate) (58). Use of this formula to derive transition rates is not entirely accurate, with the accurate derivation necessitating solving Kolmogorov equations (59). Though solutions have been published for conversions from rates to probabilities for certain two, three and four-state models, transformations are based on "simpler" three-state and four-state models that have at most one backward transition probability. With multiple backwards transitions, as in the case of this model, published procedures cannot be employed and are extremely complicated algebraically (59). Given the relatively short cycle length of 4 weeks employed, use of the simple formula to convert between probabilities and rates was considered sufficient. This is consistent with the approach adopted in the reslizumab submission (60).

To ensure transition probabilities added up to 1 (particularly in sensitivity analyses) each transition probability was constrained at a maximum of 1- transition probabilities to more severe states (see

Appendix O. Estimation of Transition Probabilities for further details on calculations).

8.2.2.4.2 Severe Exacerbations

Table 37 summarises the relative efficacy in reducing severe exacerbations for all biologic patients versus dupilumab in the population of patients outlined in Table 35 without steroid dependency.

Table 37. Relative Rates of Experiencing Severe Exacerbations versus Dupilumab – All Patients Not on Maintenance OCS

Treatment	Mean	95% Lower	95% Upper
	(Child population) Norman et al. 2013(61)		
Background Therapy Alone	[redacted]	[redacted]	[redacted]
Omalizumab + Background Therapy	[redacted]	[redacted]	[redacted]
Mepolizumab + Background Therapy	[redacted]	[redacted]	[redacted]

Note: ¤, assumed as same RR as in adult/adolescent population (Bateman 2020)

For the model background therapy alone was derived from post-hoc analyses of VOYAGE whilst assumptions were made regarding the relative effects for omalizumab and mepolizumab for moderate exacerbations (Table 38).

Table 38. Relative Rates of Experiencing Moderate Exacerbations – Exploratory Analyses

Comparator	Mean	95% Lower	95% Upper
		All Patients	
Background therapy	[redacted]	[redacted]	[redacted]
Omalizumab	[redacted]	[redacted]	[redacted]
Mepolizumab	[redacted]	[redacted]	[redacted]

Source:

a. Estimated based on transition probabilities; Displayed for completeness; Not used in calculations

b. Moderate exacerbation assumed equivalent to dupilumab, Lower and Upper CI assumed

8.2.2.4.3 Uncontrolled Asthma

The RR of transitioning to the 'Uncontrolled asthma' state was not a reported outcome in the clinical trials; therefore, this was not examined in the indirect comparisons. Whilst data on ACQ versus mepolizumab were available, assumptions would be needed to convert the mean difference in ACQ to a RR of experiencing uncontrolled disease. In addition, the inclusion of alternative transition probabilities to uncontrolled disease based on the presence of severe exacerbations must be considered. Given the severe

exacerbation rate would vary between dupilumab and mepolizumab (in favour of dupilumab), to avoid double-counting it was considered more appropriate to assume that transitions to uncontrolled disease (from any health state) were equivalent between treatments, and that differences would be driven by differences in exacerbations. A RR of 1 was therefore implemented, which was varied by 20% in sensitivity analyses to determine the influence of this assumption.

For the model, relative rates of uncontrolled asthma for background therapy, omalizumab and mepolizumab are shown in Table 39 for all patients and responders.

Table 39. Relative Rates of Uncontrolled Asthma – Exploratory Analyses (Child)

Comparator	Mean	95% Lower	95% Upper
		All Patients	
Background Therapy[a]	[redacted]	[redacted]	[redacted]
Omalizumab[b]	[redacted]	[redacted]	[redacted]
Mepolizumab[b]	[redacted]	[redacted]	[redacted]
		Responders	
Omalizumab[b]	[redacted]	[redacted]	[redacted]
Mepolizumab[b]	[redacted]	[redacted]	[redacted]

Source:

a. Estimated based on transition probabilities; Displayed for completeness; Not used in calculations
b. Assumed equivalent to dupilumab, Lower and Upper CI assumed

8.2.2.4.4 Proportion of Patients Achieving Response

Assessment of response have been excluded in the base-case, due to uncertainty on the RRs established.

8.2.2.5 Adverse reaction outcomes

The safety data for the different comparators can be found in the sections 7.1.2.1.2, 7.1.2.2.2, and 7.2.2.2.2. In previous submission and recommendation of dupilumab for adult asthma, DMC stated that dupilumab, omalizumab, and mepolizumab was assessed to be equivalent in terms of adverse events and that these AEs have not been considered adverse events requiring hospital treatment (14, 62). For this reason, AEs is not included in this economic evaluation.

8.2.2.5.1 Asthma-related Death

Severe exacerbations and asthma deaths are rare events in clinical trials, making estimations of mortality from trials difficult. The randomised treatment period of the QUEST trial lasted 52 weeks, and altogether nine deaths occurred in the study. The treatment period of the VOYAGE trial also lasted 52 weeks and no death occurred during the study. In assessments of previous monoclonal antibodies, mortality was informed based on published literature, due to these reasons. A corollary to this is that the same

probabilities of dying are applied for all comparators in the model, with differences in life expectancy driven by differences in rates of exacerbations. The model uses varying risks of asthma-related mortality depending on the type of severe exacerbation and on age.

Several UK and US studies were identified assessing the risk of mortality after an exacerbation or hospitalisation, with three studies, being systematically used among submissions and economic evaluations (Table 137, Appendix T. Asthma-related Mortality). Mortality estimates from observational studies were heterogeneous, with estimates varying from 0.02 to 2.48 per 100 patients, depending on age, population considered, and definition used. None of the studies explicitly considers a population of uncontrolled persistent asthma patients. Thus, the applicability of these studies to the whole uncontrolled persistent asthma population is limited. Previous models and assessment bodies have approached heterogeneity by combining evidence from multiple observational studies, regularly concluding that all studies considered had limitations and that considerable uncertainty remained about the mortality associated with severe persistent asthma (see Appendix T. Asthma-related Mortality for further details).

8.2.2.5.2 Fatality Rate Associated with Exacerbations Leading to Hospitalisation

Asthma-related mortality in children, was informed by the study by Watson et al. 2007, however, the study provided separate estimates for ages 0–11, 12–16 and 17–44. Therefore, the following calculations were applied in order to derive a mortality estimate for hospitalised exacerbations in patients aged 0–11 whilst using consistent sources of data.

Firstly, a single probability of death for ages 18–44 was calculated (0.00165) from a study by Roberts et al. data (used in the adult/adolescent model, see Appendix L Adult and adolescent population for economic assessment), by pooling data for ages 18–24, 25–34, and 35–44. Secondly, the same correction by a factor of 2.5 as in the NICE appraisal of benralizumab was applied to this estimate that was based on Roberts et al. (i.e., 0.00165/2.5 = 0.00066).

Finally, the ratio of case fatality rates between ages 0–11 and ages 17–44 (0.000973/0.003827 = 0.2543) and between ages 12–16 and ages 17–44 (0.003189/0.003827 = 0.8332) observed in Watson et al. was calculated and it was assumed that the same ratios could be applied to the Roberts et al. estimate for ages 18–44 (itself assumed to be applicable to ages 17–44) in order to estimate the probability of death for ages 0–11 (which was subsequently assumed to be applicable to patients aged 6–11 in the model). For example, for adolescents, this can be summarised as:

$$Prob(Death)(Hosp)_{12\text{-}17} = \frac{Prob(Death)\ Watson_{12\text{-}16}}{Prob(Death)\ Watson_{17\text{-}44}} \times \frac{Prob(Death)\ Roberts_{18\text{-}44}}{2.5}$$

$$Prob(Death)(Hosp)_{12\text{-}17} = 0.8332 \times \frac{0.00165}{2.5} = 0.000548$$

Table 40. Age Fatality Rates Associated with Exacerbations Leading to Hospitalisation in the Model

Age Group	Base Case(65)	
	%	N*
6–11 Years	0.02%	2,115†

12–17 Years	0.05%	403§
18–24 Years	0.06%	2,420
25–34 Years	0.06%	2,420
35–44 Years	0.08%	2,420
45–54 Years	0.30%	628
55–64 Years	1.81%	521
65–74 Years	4.54%	689
75+ Years	4.54%	689

* N values for ages 18+ were estimated based on 4,258 admissions (based on BTS Asthma Audit), utilising the age distribution of asthma admissions in the source studies.
† N obtained by applying the ratio of asthma admissions between ages 0–11 and ages 17–44 in Watson et al. 2007 to the N calculated (i.e., 2,420) from BTS Asthma Audit and Roberts et al. for ages 18–44.
§ N obtained by applying the ratio of asthma admissions between ages 12–16 and ages 17–44 in Watson et al. 2007 to the N calculated (i.e., 2,420) from BTS Asthma Audit and Roberts et al. for ages 18–44.
†† N obtained by applying the ratio of asthma admissions between ages 0–11 and ages 17–44 in the updated analysis of the CHKS database to the N calculated (i.e., 2,518) from BTS Asthma Audit and updated analysis of CHKS for ages 18–44.
§ N obtained by applying the ratio of asthma admissions between ages 12–16 and ages 17–44 in the updated analysis of the CHKS database to the N calculated (i.e., 2,518) from BTS Asthma Audit and updated analysis of CHKS for ages 18–44.

8.2.2.5.3 Fatality Rate Associated with Exacerbations Leading to ER Visit or Office Visit

A further challenge arose relating to the identified asthma-related mortality data from the population studied in each of the studies (in Table 137, appendix R), i.e., patients hospitalised for asthma. This meant that estimates identified from these studies could only be applied to patients experiencing severe exacerbations leading to hospitalisation. The National Review of Asthma Deaths (NRAD) in the UK reported that only 10% of people with asthma-related death had been treated in hospital within the 28 days immediately before having the asthma attack that caused their death (70). Cases of asthma attacks treated in primary care before leading to death as well as cases that had not received treatment were reported (71). Risk of mortality in patients experiencing severe exacerbations not leading to hospitalisation is therefore also included in the model.

To estimate the risk of mortality in patients experiencing exacerbations that do not lead to hospitalisations, data from an in-depth scrutiny of 195 people who were classified with asthma as the underlying cause of death in the UK were used in the benralizumab submission to NICE (Table 41)(70), following methods used in the mepolizumab submission to NICE.(64)

Table 41. Location of Deaths Due to Asthma (UK)[70]

Location Of Death	Number	%	Assumed Setting(70)
Home	80	41.03%	OCS use
Nursing Home	5	2.56%	OCS use
Hospital, Pre-hospital Arrest (on the Way to Hospital)	45	23.08%	ER death
Hospital, Arrest in Hospital	59	30.26%	Hospital death
Holiday	4	2.05%	OCS use
Other	2	1.03%	OCS use

Based on the distribution of treatment of severe exacerbations in the pooled SIROCCO/CALIMA trials of benralizumab and based on the location of death reported in the NRAD study (Table 41), the following were estimated:

The probability of death from any exacerbation as:

$$P_{(Death|Exacerbation)} = \frac{P_{(Death|Hospital)} \times P_{(Hospital|Exacerbation)}}{P_{DeathsOccuringInHospital}}$$

The probability of death from an exacerbation requiring an ER visit as:

$$P_{(Death|ER\ visit)} = \frac{P_{(Death|Exacerbation)} \times P_{DeathsOccuringInER}}{P_{(ER|Exacerbation)}}$$

The probability of death from an exacerbation requiring OCS only as:

$$P_{(Death|OCS\ burst)} = \frac{P_{(Death|Exacerbation)} \times P_{DeathsRequiringOCS}}{P_{(OCS|Exacerbation)}}$$

As mentioned earlier, the resulting probabilities of death for the different settings of treatment of severe exacerbations were subsequently divided by a factor of 2.5 by the ERG (apart from hospitalised exacerbations for the 65+ age group and non-hospitalised exacerbations for the 45+ age group as no relevant sources could be identified for those during the benralizumab appraisal). The revised estimates (Table 42) were subsequently accepted by the NICE committee and these were used in the base-case analysis in the UK dupilumab model.

Regarding children and adolescents, the same approach as the one used in adults described above was applied. The same calculations to the mortality data reported by Watson et al. for the 0–11 and 12–16 age bands and assumed that those would be applicable to patients aged 6–11 and 12–17 in the model, respectively. The same correction by a factor of 2.5 as in the NICE appraisal of benralizumab was applied for adults aged <45 years old in order to derive the final values used in the model. Note that for adolescents (12–17 years old), this was the methodology adopted in the scenario analysis for adolescents presented in response to the ACD as part of the NICE appraisal of dupilumab in adults/adolescents.

Table 42. Probability of Acute Death after a Severe Exacerbation Used in the Model

	% of Severe Exacerbations That are Fatal (in Each Treatment Setting)					
	Office Visit		ER Visit		Hospitalisation	
Age Band	**%**	**N**	**%**	**N**	**%**	**N**
6–11 Years	0.005%	91	0.03%	45	0.02%	2,115
12–17 Years	0.02%	91	0.11%	45	0.05%	403
18–24 Years	0.02%	91	0.13%	45	0.06%	2,420
25–34 Years					0.06%	2,420
35–44 Years					0.08%	2,420
45–54 Years	0.32%	91	2.05%	45	0.30%	628
55–64 Years					1.81%	521
65+ Years					4.54%	689

Sources:
For ages 18+: NICE Benralizumab Submission; ERG Base Case;(65) N's for Office Visit and ER visit were based on the number of deaths observed in each setting in NRAD.(70) These were used in PSA and DSA to vary mean estimates, thus, a low sample size was chosen to reflect uncertainty in estimates. N's for hospitalisations were based on BTS Asthma Audit admissions (N=4,258) distributed based on age distribution in Roberts et al. 2013.
For ages <18:
For Office visit and for ER visit: calculated following the same approach as in NICE TA565, Benralizumab for older age bands, i.e., based on Watson et al. 2007 and NRAD 2014 and applying the same adjustment as in ERG base case for older age bands in NICE TA565, Benralizumab - ERG report (data for ages 0–11 and 12–16 in Watson et al. 2007 were used; assumed applicable to ages 6–11 and 12–17 here, respectively); N's for Office Visit and ER visit were based on the number of deaths observed in each setting in NRAD.(70) These were used in PSA and DSA to vary mean estimates, thus, a low sample size was chosen to reflect uncertainty in estimates.
For hospitalisations: calculated from the data for ages 18–44 in Roberts et al. 2013 by applying the same ratios as observed between ages 0–11 and ages 17–44 and between ages 12–16 and ages 17–44 in Watson et al. 2007 (assumed to be applicable as ratios between ages 6–11 and 18–44 and between ages 12–17 and 18–44 here, as Roberts et al. did not report data for ages <18); N's obtained by applying the ratios of asthma admissions between ages 0–11 and ages 17–44 and between ages 12–16 and ages 17–44 in Watson et al. 2007 to the N calculated (i.e., 2,420) from BTS Asthma Audit and Roberts et al. for ages 18–44.

8.2.2.5.4 Other-cause Death

General population life tables for Denmark, provided by Statistics Denmark, are used to estimate the age- and gender-specific risk of background death. Life tables are adjusted to exclude asthma-related deaths from the general population mortality data (and therefore avoid double-counting of asthma-related deaths in the model) by removing the proportions of deaths (by age band) that were related to asthma from the life table values. For the model, Danish data from Statistics Denmark was identified and is used for the proportion of total deaths that are asthma-related (Table 43).

Table 43. Proportions of Total Deaths that are Asthma Related, Denmark 2010-2012

Age Band	Male	Female
0-15 Years	0.00%	0.00%
16-24 Years	0.00%	0.00%
25-34 Years	0.00%	1.10%
35-44 Years	0.40%	0.70%
45-54 Years	0.30%	0.20%
55-64 Years	0.00%	0.20%
65-74 Years	0.00%	0.10%
75-84 Years	0.10%	0.10%
85 Years and Above	0.10%	0.10%

Source: Statistics Denmark(39); Sygdomsbyrden i Danmark 2015, Sundhedsdatastyrelsen (72).

8.3 Extrapolation of relative efficacy

Non-applicable. No extrapolation of relative efficacy.

8.3.1 Time to event data – summarized:

Non-applicable, no time to event data used.

8.4 Documentation of health-related quality of life (HRQoL)

8.4.1 Overview of health state utility values (HSUV)

Structure of Utilities

Changes in HRQoL resulting from add-on asthma treatment can be quantified by applying utility values to different health states. As for the adult/adolescent dupilumab model, the adapted model uses varying utility values for the following health states:

- No exacerbation states
    - Controlled asthma states
    - Uncontrolled asthma state
- Moderate exacerbation state
- Severe exacerbation state
    - Severe exacerbation – Office visit
    - Severe exacerbation – ER visit

- Severe exacerbation – Hospitalisation

In addition, the model allows for utilities to be adjusted based on treatment, by specifying an increase in utility associated with each comparator in the model. A treatment utility increment is applied to capture additional benefits associated with treatment in the child population. Conversely, in the five-sub-state model, asthma control is explicitly modelled, and different utilities are applied to patients with and without asthma control.

8.4.2 Health state utility values used in the health economic model

Utility values associated with the control-based states were informed from the clinical trials in the base case.

EQ-5D-Y values were obtained from post-hoc analyses of the LIBERTY, and EQ-5D-5L from the QUEST trials.

An analytical dataset was created and including one record per patient per visit, with observed utility value and time-dependent indicators of:

- Severe exacerbation (1, if start of severe exacerbation date ≤utility visit date ≤end of severe exacerbation date, 0 otherwise)
- Moderate exacerbation (1, if start of moderate exacerbation date ≤utility visit date ≤end of moderate exacerbation date, 0 otherwise)
- Controlled asthma (1, if patient is not experiencing exacerbation and ACQ-7 is non-missing and ACQ-7 score at utility visit is <1.5, 0 if patient is in severe or moderate exacerbation and ACQ-7 is non-missing and ACQ-7 score at utility visit is ≥1.5
- Uncontrolled asthma (1, if patient is not experiencing exacerbation and ACQ-7 is non-missing and ACQ-7 score at utility visit is ≥1.5, 0 if patient is not in severe or moderate exacerbation and ACQ-7 is non-missing and ACQ-7 score at utility visit is <1.5

Mapped values from the EQ-5D-5L to the DK EQ-5D-5L(73) and EQ-5D-Y to the DK EQ-5D-3L(74) and used in the economic model for the control-defined states are shown below (see Table 44). Further description of the mapping is provided in Appendix I.

Table 44. Trial-based mapped EQ-5D utilities base case for all three subgroups

Health State	LIBERTY ASTHMA VOYAGE – EMA Population		LIBERTY ASTHMA QUEST – EMA Population	
	Mean	SE	Mean	SE
Trial-based EQ-5D – Severe allergic asthma				
Controlled Asthma	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled Asthma	[redacted]	[redacted]	[redacted]	[redacted]
Trial-based EQ-5D – Severe eosinophilic asthma				
Controlled Asthma	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled Asthma	[redacted]	[redacted]	[redacted]	[redacted]
Trial-based EQ-5D – Severe asthma with elevated FeNO				
Controlled Asthma	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled Asthma	[redacted]	[redacted]	[redacted]	[redacted]

8.4.2.1 Utility Values Associated with Exacerbations

Disutility is applied to patients having a severe asthma exacerbation to capture the impact of these events on a patient's quality of life to the utility of uncontrolled asthma. Utility decrements from Lloyd et al. were also used for exacerbation-related disutilities for the Child cohort in the Danish model. Lloyd et al. (2007)(75) was used for the child and a QUEST post-hoc analysis was used for the adult/adolescent inputs in the Danish model (Table 45 and Table 46).

Table 45. Utilities/Disutilities Associated with Exacerbations – Child population

Type of Exacerbation		Utility Decrements Based on Lloyd et al. (2007)(75)	
		Mean	SE
Moderate Exacerbation		-0.050	0.013
Severe Exacerbation	Office Visit	-0.100	0.025
	ER Visit	-0.100	0.025

Hospitalisation	-0.200	0.050

Source: Severe exacerbation: Lloyd et al. 2007, Table 2; ED visit estimate is assumed same as office visit ('exacerbation with oral steroids' in the source) estimate; Moderate exacerbation: assumption

Table 46. Utilities/Disutilities Associated with Exacerbations – Adult/Adolescent population

Type of Exacerbation	Utility Decrements Based on QUEST post hoc analyses	
	Mean	SE
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: QUEST post hoc analyses, Utility analysis: Summary Statistics, 4 Jul 2018, ITT Population

8.4.2.1.1 Duration of Exacerbation Utility/Disutility

Utilities (or disutilities) associated with exacerbations are applied for the duration of the exacerbation (by type), using duration data obtained via post-hoc analyses of the dupilumab clinical trials for each treatment arm and using external data from Lloyd et al. 2007(75). See Table 47 for applied durations of exacerbations.

Table 47. Duration of Exacerbation Utility/Disutility (in days)

Type of Exacerbation	Background therapy only		Add-on treatments	
	Mean	SE	Mean	SE
Child population				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Source: Children: Assumption based on Lloyd et al. 2007; Adults/adolescent population: QUEST, post-hoc analysis, ITT population(76)

8.4.2.2 Age-adjusted utilities

Utilities in the model are age-adjusted, based on the mean age of the cohort at a given time in the model. In line with the DMC guidelines, (77), the age adjustments are applied by using a multiplicative method: the decrement (or increment) is estimated as the difference between the utility, in the general population, for the age band within which the current mean age of the cohort falls and the utility, in the general population, for a 'reference' age band, which is the one that comprises the mean age of the cohort at baseline. The general population utility data used for these calculations is sourced from the Danish Medicines Council website,(78) as stipulated in the DMC guidelines. The Danish inputs, which are recommended to be used by the DMC, are shown in Table 48, with equal utility for age 6-17 as age 18-29 being assumed.

Table 48. General Population Utility Values by Age Band Used to Estimate Utility Decrements Due to Ageing

Age Band	Mean	SE
6–17 Years	0.871	0.174
18–29 Years	0.871	0.174
30–39 Years	0.848	0.170
40–49 Years	0.834	0.167
50–69 Years	0.818	0.164
70–79 Years	0.813	0.163
80-100 Years	0.721	0.144

8.5 Resource use and costs

Costs and resource use vary dependent on the administered treatment and on health states. The model includes direct medical costs, as well as transport costs and time spent on treatment by patients and relatives, consistent with the limited societal perspective as described in the DMC guidelines (77). Table 49 presents the cost components for consideration in the model.

Table 49. Cost Categories and Frequency

Cost category	Frequency	Health state(s)
Drug acquisition costs (add-on treatment)	Per cycle	All live health states on add-on treatment
Drug acquisition costs (background therapy)	Per cycle	All live health states
Drug administration costs	Per cycle	All live health states on add-on treatment
Monitoring costs (following drug administration)	Per administration (applied for a certain number of cycles, see the Monitoring cost-section)	All live health states on add-on treatment
Routine visit and disease management costs	Per cycle	Non-exacerbation health states
Exacerbation costs (including disease management)	Per cycle	Exacerbation health states
mOCS-related costs (adults/adolescents on mOCS only)	One-off for acute phase of AEs; per cycle for OCS drug cost and for long-term phase of AEs	All live health states
Transport costs and time spent on treatment by patients and relatives	Per cycle	All live health states on add-on treatment
Cost offsets associated with atopic comorbidities	Per cycle	All live health states
Indirect productivity costs (placeholder)	Per cycle	TBD

As described in the HCC section, applying an HCC to estimate drug costs may underestimate the costs associated with treatments that are administered every four weeks (the duration of a model cycle). In the base case, no HCC is applied to such treatment, mepolizumab, since the proportion of the cohort accumulating drug costs in this case is known as state membership in the beginning of the cycle (Table 50). Regarding omalizumab, which may be administered every two weeks, every four weeks, or every eight weeks, it is assumed that an HCC is applied in the base case.

Table 50. Approach to Application of Drug-related Costs

Treatment	Approach to Application of Drug-related Costs
Dupilumab (alone)	Half-cycle corrected state membership
Background therapy alone	Half-cycle corrected state membership
Omalizumab (alone)	Half-cycle corrected state membership
Mepolizumab (alone)	State membership at the beginning of the cycle

Unit costs for healthcare resource use items are derived from standard public sources in Denmark and supplemented by studies identified in the published literature. For instance, costs for healthcare personnel, procedures and hospitalisations were sourced from the DMC catalogue of unit costs (79). The Danish Medicines Agency database was searched for costs of medications. Whenever the data extracted from the published literature or from publicly available databases corresponded to costs applicable to

earlier years than 2021, they were inflated to 2021 Danish krone, using the consumer price index without energy available on the Statistics Denmark website (www.statistikbanken.dk), as stipulated in the DMC guidelines (77).

8.5.1 Pharmaceutical costs

For all pharmaceuticals administered in the model, pharmacy purchase prices (PPP) have been used. These were fetched from Medicinpriser.dk (80).

8.5.1.1 Biologics

The PPP for the biologics were fetched from Medicinpriser.dk (80) on the 14 Jan 2022 and are presented in Table 52. As the model has a time-horizon stretching over a life-time, the child patients will grow and dosing will change accordingly, further at one point the population will move from a child dosing scheme to an adult. This is applicable for both omalizumab and dupilumab and will be described below.

Dupilumab

The administration schedule of dupilumab expected for children aged 6-<12 years in Danish clinical practice, and in the base-case, is based on the following:

- Body weight ≥15-≤60 kg: 300 mg every 2 weeks
- Body weight >60 kg: 200 mg every 2 weeks

The proportions of the child cohort falling under each of two weight groups at model start: ≤30 kg vs. >30 kg (or ≤60 kg vs. >60 kg when the alternate 300 mg Q2W dosage is selected), is based on the baseline characteristics from the VOYAGE study.

Switching from child dosing to adult/adolescent dosing will be based on the data from LIBERTY QUEST/VENTURE trials when patients turn 12 years old onwards.

The administration schedule of dupilumab will for adults/adolescents (≥12 years) be:

- For adults and adolescents not on mOCS (population of the Liberty Asthma QUEST trial): 200 mg every 2 weeks

Depending on weight, patients are treated with either 200mg, and 300mg dupilumab. The dose of 200mg vial is found at a price of DKK 4,202.42 per dose on medicinpriser.dk (cost per pack: 8,404.83). The dose of 300mg is found at a cost of DKK 4,449.95 (cost per pack: DKK 8,899.90). The dosing schemes for all the populations are also illustrated in Table 51 and the cost per dose/vial can be found in Table 52.

Table 51 Dupilumab dosing schemes

Population	Dose (mg)	Number of administrations per model cycle (4 weeks)	Source
Children ≥15-≤60 kg	300	1	VOYAGE

Population	Dose (mg)	Number of administrations per model cycle (4 weeks)	Source
Children >60 kg	200	2	VOYAGE
Adults/adolescents	200	2	QUEST
	300	2	QUEST, VENTURE

Omalizumab

The administration schedule of omalizumab is dependent on weight and IgE levels, rather than age, and dosages range from 75 to 600 mg Q4W. The dosing scheme illustrating the specific dosing by weight and IgE levels, can be seen in N is used to calculate alpha & beta for all parameters that use a beta distribution. N should not be interpreted as a standard error

Appendix K. The cost of omalizumab is found on medicinpriser.dk at a price of DKK 1,277.01 for a 75mg vial and DKK 2,128.72 for a 150mg vial. Cost per dose/vial can be found for all treatments in Table 52.

Mepolizumab

The administration schedule of mepolizumab was for children aged 6 to <12 years 40mg and 100mg for adults/adolescents Q2W. The cost of mepolizumab is found on medicinpriser.dk at a price of DKK 7,772.89 for a 100mg vial. A 40 mg vial is not available in Denmark. Cost per dose/vial can be found for all treatments in Table 52 Pharmaceutical costs used in the model Table 62.

Table 52 Pharmaceutical costs used in the model

Drug	Dose (mg)	Packing (unit)	Cost per pack	Cost per dose	Source
Dupilumab	200	2 syringes	DKK 8,404.83	DKK 4,202.42	Medicinpriser.dk (Date 14 Jan 2022)
Dupilumab	300	2 syringes	DKK 8,899.90	DKK 4,449.95	Medicinpriser.dk (Date 14 Jan 2022)
Omalizumab	75	1 syringe	DKK 1,277.01	DKK 1,277.01	Medicinpriser.dk (Date 14 Jan 2022)
Omalizumab	150	1 syringe	DKK 2,128.72	DKK 2,128.72	Medicinpriser.dk (Date 14 Jan 2022)
Mepolizumab	100	1 syringe	DKK 7,772.89	DKK 7,772.89	Medicinpriser.dk (Date 14 Jan 2022)

8.5.1.2 Background therapy

To estimate the acquisition costs related to background therapy, the proportions of patients receiving each type of background treatment (e.g., ICS, LABA, etc.) are included in the model. It is assumed that the same proportions applied to all patients in the model regardless of whether they received a monoclonal antibody or not and regardless of which monoclonal antibody. In the adult/adolescent model, the proportions of patients receiving each background treatment were based on data on controller medications at randomisation in the Liberty Asthma QUEST and VOYAGE trials, pooling data across the dupilumab and corresponding placebo arms. For the child population, a similar approach is applied in the model, using data on controller medication use at randomisation in the Liberty Asthma VOYAGE trial. The proportions of use of the different components of background therapy are therefore based on the distribution of drugs received by patients in the pivotal dupilumab trials, separately for the child population and for the adult/adolescent population. Although treatment may affect controller medication, this is not considered in the model as a simplifying approach, given that the cost of background therapy is expected to be minimal as compared to other costs considered, thus having little effect on results. Unit costs for background therapy and biologic add-on treatments obtained from medicinpriser.dk are implemented in the model, see Table 53. For controller/reliever medications, multiple costs were available; several different active ingredients are also available (e.g., for ICS, LABA and ICS/LABA combination inhalers). For conservatism, the active ingredient resulting in the lowest daily cost when combined with average dose used in the clinical trial was extracted, following the approach adopted in the adult/adolescent model.

Table 53. Background therapy drugs: Price and Dosing

Background Therapy Drugs	Route of administration	Strength (mg)	Package Size (number of tablets/doses)	List price per pack (DKK)	Cost per mg (DKK)	Child Dosage (mg) [a]	Adult/Adolescent Dosage (mg) [b]	Overall Dosage
Medium-dose ICS	Inhaled	0.40	200	212.50	2.66	0.3276	Inhaled	0.4763
High-dose ICS	Inhaled	0.40	200	212.50	2.66	0.8620	Inhaled	0.9649
Medium-dose ICS/LABA (combination inhaler)	Inhaled	0.25	60	44.30	2.95	0.3335	Inhaled	0.4975
High-dose ICS/LABA (combination inhaler)	Inhaled	0.25	60	44.30	2.95	0.6465	Inhaled	0.9780
LABA	Inhaled	0.025	120	180.00	60.00	0.0174	Inhaled	0.0222
LTRA	Oral	10	28	9.10	0.03	5.3000	Oral	9.9000
LAMA	Inhaled	0.0025	30	212.29	2,830.53	0.0000	Inhaled	0.0129
Theophylline	Oral	400	100	124.00	0.00	0.000	Oral	365.600
SABA[c]	Inhaled	0.10	200	19.00	0.95	0.8000	Inhaled	0.8000

Source: [a] VOYAGE post hoc analysis, ITT, 1 Oct 2021, [b] QUEST post hoc analysis, Patient characteristics, 3 Jul 2018, ITT population, [c] Assumption based on NICE TA431, Mepolizumab – MS, Table 119 (page 214), Medicinpriser.dk

8.5.2 Treatment administration costs

No administration cost is assumed for background therapy drugs, as these treatments are either inhaled or taken orally. Dupilumab is administered by s.c injection and may be administered by a healthcare professional or may be self-administered at home after receiving appropriate training. Administration of other subcutaneous add-on treatments, omalizumab and mepolizumab, may be carried out by a healthcare professional or may be self-administered at home. Both treatments are indicated for self-administration, but as with dupilumab, some patients may be unable to self-administrate. The model therefore included input fields that define the proportion of patients requiring administrations in each setting: hospital outpatient or self-administration. The proportion of patients who receive dupilumab and comparators in each of the settings were confirmed via consultation with clinicians. A one-off training cost for self-administration of subcutaneous treatments is also considered in the model in addition to the unit cost associated with each administration, where applicable.

In the model, s.c administrations are assumed to be carried out by a specialist nurse for 10 minutes. Unit costs for administration of monoclonal antibodies in Denmark were collected from the DMC catalogue of unit costs. It was assumed in the model that 100% of all would get their treatment with dupilumab administrated at the hospital, see Table 54. Costs of administration are calculated by multiplying the cost of nurse and secretary time by the duration of administration.

Table 54. Resource use associated with drug administration (child population)

Treatment	Duration (Minutes per Administration)	% Administered by Healthcare Professional			% self-Administered	
		Office Visit	Home Visit	Hospital Out-patient	%	N
Dupilumab (alone)	10 mins	0.0%	0.0%	100.0%	0.0%	100
Background therapy alone						
Omalizumab (alone)	10 mins	0.0%	0.0%	90.0%	10.0%	100
Mepolizumab (alone)	10 mins	0.0%	0.0%	100.0%	0.0%	100

Unit costs for administration of monoclonal antibodies in Denmark were collected from the DMC catalogue of unit costs (79). Those applied in the model are summarised in Table 55. Based on these unit costs, the proportions of patients receiving their treatment in each setting (Table 54) and the number of administrations per cycle (section 8.5.1.1), the administration costs per cycle were calculated for each treatment.

Table 55. Drug administration: Unit Costs

	Unit Cost	Source
s.c. administration		
Hospital outpatient	DKK 131.16 per administration	Calculated from: Cost per hour of a senior nurse: https://www.krl.dk/#/sirka; Senior nurse - '276 Syge- og sundhedspers., ledere, Regioner' Duration per administration (10 minutes): NICE TA431, mepolizumab – manufacturer submission, Table 121 (page 215); NICE TA479, reslizumab – manufacturer submission (page 209); Norman et al. 2013, Table 52(60, 61, 64)
Self-administration training	DKK 1,083.441 (one-off cost)	Cost per hour of a senior nurse https://www.krl.dk/#/sirka; Senior nurse - '276 Syge- og sundhedspers., ledere, Regioner' Cost per hour of outpatient visit to Pulmonologist, duration of visit 15 mins.: https://www.krl.dk/#/sirka; Specialist - '100 Sygehuslæger (hon.løn)'

In Denmark, resource use for office visits and home visits is not available Costs of administration are calculated by multiplying the cost of nurse and secretary time by the duration of administration.

8.5.3 Monitoring cost

The model follows the assumption of costing 15 minutes per hour of specialist nurse's time that was used in previous models (Table 56). Given the heterogeneity in the assumptions used in past submissions for other monoclonal antibodies, a conservative approach is adopted by assuming that 15 minutes of specialist nurse time would be necessary for monitoring after the first three administrations for the other monoclonal antibodies, and that no monitoring would be required for subsequent administrations (61, 64, 81). The requirements for monitoring and resource use associated with it for add-on biologic treatments in Denmark were validated during consultation with KOLs.

Table 56. Monitoring Unit Cost

Unit Cost	Source

Monitoring by senior nurse	DKK 786.94 per working hour	https://www.krl.dk/#/sirka; Senior nurse - '276 Syge- og sundhedspers., ledere, Regioner'

Based on the duration of monitoring and on the unit cost for specialist nurse time (Table 56), the cost of monitoring per administration for initial administrations and the cost of monitoring per administration for subsequent administrations are calculated for each of the add-on biologics.

A 30-minute duration for the initial administration is assumed for children with a 15-minute duration of monitoring for subsequent visits after discussion with KOLs. These durations were combined with the monitoring cost for a nurse to calculate monitoring costs. For children an initial 3 visits is assumed, with the cost of the monitoring calculated based on the hourly rate for a nurse, see Table 57.

Table 57. Monitoring Unit Cost as applied in the model

	Initial Administration Unit Cost	Subsequent Administration Unit Cost	Source
Monitoring by nurse for Children	DKK 554 per working hour; costed at 30 minutes per hour (= DKK 277 per hour)	DKK 554 per working hour; costed at 15 minutes per hour (= DKK 138.50 per hour)	Medicinrådet Værdisætning af enhedsomkostninger,vers 1.2

8.5.3.1 Routine visits and Disease Management Costs

Day-to-day management of asthma incurs costs, such as routine general practitioner (GP) or nurse visits to assess symptoms and optimise treatment, complementary tests and procedures, and specialist visits (82).

The resource use associated with routine visits and disease management based on expert opinion from a Danish clinician(83). The Danish KOL provided input to the type of visits and tests, and the frequency to which the patients are monitored.

Disease management may also vary between young children and adults/adolescents. Therefore, the model allows to specify the type of resources needed and the frequency of use of these resources separately for each of these two age groups. The routine care resource use data used in the Danish base case is shown in Table 58 with the routine care costs shown in Table 59.

Table 58. Routine Care Resource Use per Cycle (4 Weeks) by Level of Control

Resource	In the 'Controlled Asthma' Health State*		In the 'Uncontrolled Asthma' Health State	
	Mean	SE†	Mean	SE†
Children (6-11)				
Outpatient visits: Nurse	0.333	0.067	0.500	0.100
Outpatient visits: Pulmonologist	0.333	0.067	0.500	0.100
Spirometry and FeNO tests	0.333	0.067	0.500	0.100

Source: For controlled asthma, a monitoring visit every 12 weeks is assumed (20 min nurse, 1 hours physician to do tests, spiro, reversibility, mannitol test, FeNO, blood samples (IgE, eosinophilic status, BAT) / For uncontrolled asthma, a monitoring visit every 8th week is assumed, (20 min nurse, 1 hours physician to do tests, spiro, reversibility, mannitol test, FeNO, blood samples (IgE, eosinophilic status, BAT)

Unit costs for disease management resource use in Denmark were collected from the DMC catalogue of unit costs (79) or other publicly available sources when necessary, see Table 59.

Table 59. Routine Care Unit Costs

Resource	Unit Cost	Source
	Child population	
Outpatient visits: Nurse	DKK 185.97	Calculated from: Cost per hour: Medicinrådet Værdisætning af enhedsomkostninger,vers 1.2; Inflated to 2021; Duration of visit: elicited from Danish KOLs via expert in out/validation (20 minutes)
Outpatient visits: Pulmonologist	DKK 1,186.00	https://www.krl.dk/#/sirka; Specialist - '100 Sygehuslæger (hon.løn)'
Spirometry and FeNo tests	DKK 242.00	https://www.laeger.dk/sites/default/files/paediatri_takstkort_pr_040121_0.pdf; Performed by a specialist: 'Tillægsydelser §1, stk. 2: 2203 - Spirometri uden reversibilitetstest'

8.5.3.2 Exacerbation costs

Asthma exacerbations are associated with increased healthcare resource use and costs due to ER visits, hospitalisations, intensive care unit (ICU) stays, additional outpatient visits and rescue medication (OCS), among others (84). In the model, exacerbations are differentiated by severity (moderate vs. severe exacerbations) and by the type of resource used: exacerbations requiring treatment with OCS/a physician's office visit, exacerbations requiring an ER visit, or exacerbations requiring hospitalisation, consistent with the majority of previous models (63-65, 85-89).

The availability of sources for resource use data for Denmark were limited, and therefore a Swedish source have been used as a proxy for the estimated resource used associated with exacerbations in Denmark(90). The estimates were deemed to be likely in the Danish setting by the consulted KOL(83). See Table 60.

Exacerbation-related unit costs are calculated using Danish data alongside the resource use frequency (Table 60 and Table 61). The costs for each treatment setting for each exacerbation setting and cohort are shown in Table 62.

Table 60. Resource Use per Cycle (4 Weeks) Associated with Exacerbations

Resource	Moderate Exacerbation		Severe Exacerbation Treated with Office Visit		Severe Exacerbation Treated with ER visit		Severe Exacerbation Treated with Hospitalisation	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Outpatient visits: Nurse[b]	0.50	0.100	1.00	0.200	1.00	0.200	2.00	0.400
Outpatient visits: Pulmonologist[b]	0.50	0.100	1.00	0.200	1.00	0.200	1.00	0.200
Outpatient visits: Psychiatrist[b]	0.00	0.0	1.00	0.200	1.00	0.200	2.00	0.400

Spirometry and FeNO tests[c]	0.50	0.100	1.00	0.200	1.00	0.200	2.00	0.400
OCS[b]	0.00	0.0	150.00	30.0	300.00	60.0	600.00	120.0
Emergency room attendance[b]			1.00	0.200	0.00	0.0	1.00	0.200
Ambulance use[d]				0.25	0.050	0.050	0.25	0.050
Hospitalisation[b]							1.00	0.200

Sources: [a] Assumed the same as for severe exacerbations in office, [b] Socialstyrelsen (2018) Nationella riktlinjer för vård vid astma och KOL, [c] Internetmedicin (2019) OCS dos, [d] Assumption

Table 61. Exacerbation-related Unit Costs

Resource	Unit Cost	Source
Outpatient visits: Nurse	DKK 554.00 per visit	Medicinrådet Værdisætning af enhedsomkostninger,vers 1.2
Outpatient visits: Pulmonologist	DKK 1,186.00 per visit	https://www.krl.dk/#/sirka; Specialist - '100 Sygehuslæger (hon.løn)'
Outpatient visits: Psychiatrist	DKK 1,944.00 per visit	Hospital tariff for psychiatrist (Psykiatritakster, Ambulant) - based on 'Psykiatritakster 2021', available at: https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2021
OCS	DKK 0.08 per mg	https://www.medicinpriser.dk/default.aspx - Accessed Nov 2021
Emergency room attendance	DKK 1,732.00	DRG tariff , 04MA98 - MDC04 1-dagsgruppe, pat. mindst 7 år
Ambulance use	0.00	Assumption
Hospitalisation	DKK 14,880.00	DRG tariff, 04MA22 - Bronkit og astma, pat. 0-59 år

Table 62. Exacerbation Cost per Cycle Summary

	Child cohort when based on external source of data in children		Adult/adolescent cohort	
Treatment Setting	**Moderate Exacerbation**	**Severe Exacerbation**	**Moderate Exacerbation**	**Severe Exacerbation**
Office visit	DKK 806.99	DKK 3,569.50	DKK 806.99	DKK 3,592.25
ED visit		DKK 5,313.03		DKK 5,335.78
Hospitalisation		DKK 20,856.05		DKK 20,901.55

8.5.4 Costs of adverse events

As stated earlier, the safety profile in relation to AEs for dupilumab, omalizumab, and mepolizumab is very similar and for this reason no AEs are included in the model.

8.5.5 Patient and transportation costs

Patient costs (defined as patient costs in DMC guidelines (91)) are included in the model in line with the DMC method guidelines. The unit cost per hour is assumed to be DKK 179 in line with the DMC guidelines, see Table 63 (91).

Transportation costs are included in the model in line with DMC guidelines. Here an average rate of DKK 3.52 per km is assumed with an average distance of 28 km per hospital visit, in line with DMC's methods guidelines (Table 63) (91).

Table 63. Patient costs used in the model

Type of costs	Unit cost	Units per administration	Total cost per administration	Source
Average hourly wage	DKK 179	0.5 hours	DKK 89.5	Medicinrådet - "Værdisætning af enhedsomkostninger"
Patient transport cost	DKK 98.56	1	DKK 99	Medicinrådet - "Værdisætning af enhedsomkostninger"

In the model, transportation cost is applied at the occurrence of hospital visits, e.g. administration of a pharmaceutical.

The resource use used for patients and their relatives is calculated based on the proportion of patients receiving treatment at the hospital and at home as self-administrated, respectively (Table 54). It is assumed that the administration of all three-treatment indication is 10 minutes independent on the location of the administration. An additional 20 minutes was added to the 10 minutes of administration at the hospital in order to take waiting time into account. The time and transport cost for children is shown in Table 64.

Table 64. Resource use for transport costs and time spent on treatment by patients and relatives

Treatment	Hospital outpatient	Self-administration	Cost per treatment
Children (6-11)			
Dupilumab	DKK 191.04	DKK 0.00	DKK 191.04
Omalizumab	DKK 190.75	DKK 0.00	DKK 190.75
Mepolizumab	DKK 191.04	DKK 0.00	DKK 191.04

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8.6 Results

8.6.1 Base case overview

Table 65 Base case overview

Comparator	Severe allergic asthma subgroup: Omalizumab add-on Severe eosinophilic asthma subgroup: Mepolizumab add-on or background therapy Severe asthma with elevated FeNO: background therapy
Type of model	Markov model
Perspective	Limited societal perspective
Time horizon	Life-time
Populations	Severe allergic asthma subgroup Severe eosinophilic asthma subgroup Severe asthma with elevated FeNO subgroup
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-Y in Liberty Asthma VOYAGE and with EQ-5D-5L in Liberty Asthma QUEST. EQ-5D-Y was mapped to DK EQ-5D-3L(74) and EQ-5D-5L was mapped to DK EQ-5D-5L(73).
Treatment discontinuation	Constant long-term discontinuation rates from Liberty Asthma VOYAGE (children) and Liberty Asthma QUEST (adults/adolescents).
Included costs	Pharmaceutical costs Hospital costs Exacerbation cost Monitoring cost Patient costs

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8.6.2 Base case results

The disaggregated cost-effectiveness results for the following subgroups are presented in this section:

- Severe allergic asthma subgroup
  - Vs. omalizumab + background therapy (Table 66)
- Severe eosinophilic asthma subgroup
  - Vs. mepolizumab + background therapy (Table 67)
  - Vs. background therapy (Table 68)
- Severe asthma with elevated FeNO subgroup
  - Vs. background therapy (Table 69)

8.6.2.1 Summary of incremental cost-effectiveness results (deterministic analyses)

In the severe allergic asthma subgroup, dupilumab was dominant when compared with omalizumab + background therapy (Table 66).

In the severe eosinophilic asthma subgroup, dupilumab was dominant when compared with mepolizumab + background therapy (Table 67). When compared to background therapy alone, dupilumab has an ICER of [redacted] per incremental QALY.

In the severe asthma with elevated FeNO subgroup, dupilumab has an ICER of [redacted] per incremental QALY.

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8.6.2.2 Severe allergic asthma subpopulation

Table 66 Base case results – Child cohort, severe allergic asthma subpopulation, vs. omalizumab + background therapy

Per patient	Dupilumab + background therapy	Omalizumab + background therapy	Difference
Life years gained			
Total life years	[redacted]	[redacted]	[redacted]
In controlled asthma health state	[redacted]	[redacted]	[redacted]
In uncontrolled asthma health state	[redacted]	[redacted]	[redacted]
In moderate exacerbation health state	[redacted]	[redacted]	[redacted]
In severe exacerbation health state	[redacted]	[redacted]	[redacted]
[redacted]			
Total QALYs	[redacted]	[redacted]	[redacted]
In controlled asthma health state	[redacted]	[redacted]	[redacted]
In uncontrolled asthma health state	[redacted]	[redacted]	[redacted]
In moderate exacerbation health state	[redacted]	[redacted]	[redacted]
In severe exacerbation health state	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]			
Add-on treatment	[redacted]	[redacted]	[redacted]
Background therapy	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]
Transport costs and time spent on treatment by patients and relatives	[redacted]	[redacted]	[redacted]
Disease management costs	[redacted]	[redacted]	[redacted]
Exacerbation-related costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]

Incremental results	Dupilumab + background therapy vs. Omalizumab + background therapy
Incremental cost per life-year gained	**Dupilumab + background therapy is dominant**
Incremental cost per QALY gained	**Dupilumab + background therapy is dominant**

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8.6.2.3 Severe eosinophilic asthma subpopulation

Table 67. Base case results – Child cohort, high EOS, vs. mepolizumab + background therapy

Per patient	Dupilumab + background therapy	Mepolizumab + background therapy	Difference
Life years gained			
Total life years	[redacted]	[redacted]	[redacted]
In controlled asthma health state	[redacted]	[redacted]	[redacted]
In uncontrolled asthma health state	[redacted]	[redacted]	[redacted]
In moderate exacerbation health state	[redacted]	[redacted]	[redacted]
In severe exacerbation health state	[redacted]	[redacted]	[redacted]
[redacted]			
Total QALYs	[redacted]	[redacted]	[redacted]
In controlled asthma health state	[redacted]	[redacted]	[redacted]
In uncontrolled asthma health state	[redacted]	[redacted]	[redacted]
In moderate exacerbation health state	[redacted]	[redacted]	[redacted]
In severe exacerbation health state	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]			
Add-on treatment	[redacted]	[redacted]	[redacted]
Background therapy	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]
Transport costs and time spent on treatment by patients and relatives	[redacted]	[redacted]	[redacted]
Disease management costs	[redacted]	[redacted]	[redacted]
Exacerbation-related costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]

Incremental results	Dupilumab + background therapy vs. Mepolizumab + background therapy
Incremental cost per life-year gained	**Dupilumab + background therapy is dominant**
Incremental cost per QALY gained	**Dupilumab + background therapy is dominant**

Table 68. Base case results – Child cohort, high EOS, vs. background therapy only

Per patient	Dupilumab + background therapy	Background therapy alone	Difference
Life years gained			
Total life years	[redacted]	[redacted]	[redacted]
In controlled asthma health state	[redacted]	[redacted]	[redacted]

In uncontrolled asthma health state	[redacted]	[redacted]	[redacted]
In moderate exacerbation health state	[redacted]	[redacted]	[redacted]
In severe exacerbation health state	[redacted]	[redacted]	[redacted]
[redacted]			
Total QALYs	[redacted]	[redacted]	[redacted]
In controlled asthma health state	[redacted]	[redacted]	[redacted]
In uncontrolled asthma health state	[redacted]	[redacted]	[redacted]
In moderate exacerbation health state	[redacted]	[redacted]	[redacted]
In severe exacerbation health state	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]			
Add-on treatment	[redacted]	[redacted]	[redacted]
Background therapy	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]
Transport costs and time spent on treatment by patients and relatives	[redacted]	[redacted]	[redacted]
Disease management costs	[redacted]	[redacted]	[redacted]
Exacerbation-related costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]

Incremental results	Dupilumab + background therapy vs. Background therapy alone
Incremental cost per life-year gained	[redacted]
Incremental cost per QALY gained	[redacted]

8.6.2.4 Severe asthma with elevated FeNO subpopulation

Table 69. Base case results – child cohort, elevated FeNO, vs. background therapy

Per patient	Dupilumab + background therapy	Background therapy alone	Difference
Life years gained			
Total life years	[redacted]	[redacted]	[redacted]
In controlled asthma health state	[redacted]	[redacted]	[redacted]
In uncontrolled asthma health state	[redacted]	[redacted]	[redacted]
In moderate exacerbation health state	[redacted]	[redacted]	[redacted]
In severe exacerbation health state	[redacted]	[redacted]	[redacted]
[redacted]			
Total QALYs	[redacted]	[redacted]	[redacted]
In controlled asthma health state	[redacted]	[redacted]	[redacted]

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In uncontrolled asthma health state	[redacted]	[redacted]	[redacted]
In moderate exacerbation health state	[redacted]	[redacted]	[redacted]
In severe exacerbation health state	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
Add-on treatment	[redacted]	[redacted]	[redacted]
Background therapy	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]
Transport costs and time spent on treatment by patients and relatives	[redacted]	[redacted]	[redacted]
Disease management costs	[redacted]	[redacted]	[redacted]
Exacerbation-related costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]

Incremental results	Dupilumab + background therapy vs. Background therapy alone
Incremental cost per life-year gained	[redacted]
Incremental cost per QALY gained	[redacted]

8.7 Sensitivity analyses

To identify key model drivers and the influence of parameter uncertainty, one-way deterministic sensitivity analyses (DSA) are conducted using alternate values for model parameters. All parameters subject to parameter uncertainty are included in the sensitivity analysis. This includes transition probabilities, setting of exacerbation treatment, probabilities of asthma-related death, utility values, costs related to disease management and exacerbations. Although drug costs are not subject to parameter uncertainty, the drug acquisition cost for each treatment is also varied to understand influence on results and potential implication of a discount.

In the DSA, they are modified using high, low, and base-case values to illustrate the sensitivity of CE results to variation in these parameters. The parameters are varied using 95% CIs or a SE based on empirical data, where available, while holding all other parameters constant. Where the published study/source for parameter values did not report SEs or CIs, it is assumed that the SE is equivalent to 20% of the mean. Drug costs, monitoring costs, administration costs and disease management costs are varied ±20%. Disease management and exacerbation related costs were varied in their aggregate form (i.e. individual resource use and unit cost items were not varied one at a time). The source of variation and distribution used to determine CIs were consistent between the DSA and probabilistic sensitivity analysis (PSA).

To test the robustness of results with respect to uncertainty in the model input parameters, a PSA is performed using a second-order Monte Carlo simulation. In this analysis, each parameter subject to parameter uncertainty is assigned a probability distribution, and cost-effectiveness results associated with the simultaneous selection of random values from the distribution of each of these parameters were generated. This process is repeated for 1,000 iterations and results of the PSA were plotted on the cost-effectiveness plane (or scatter plot) and were used to calculate cost-effectiveness acceptability curves (CEACs), highlighting the probability of cost-effectiveness over various willingness to pay thresholds.

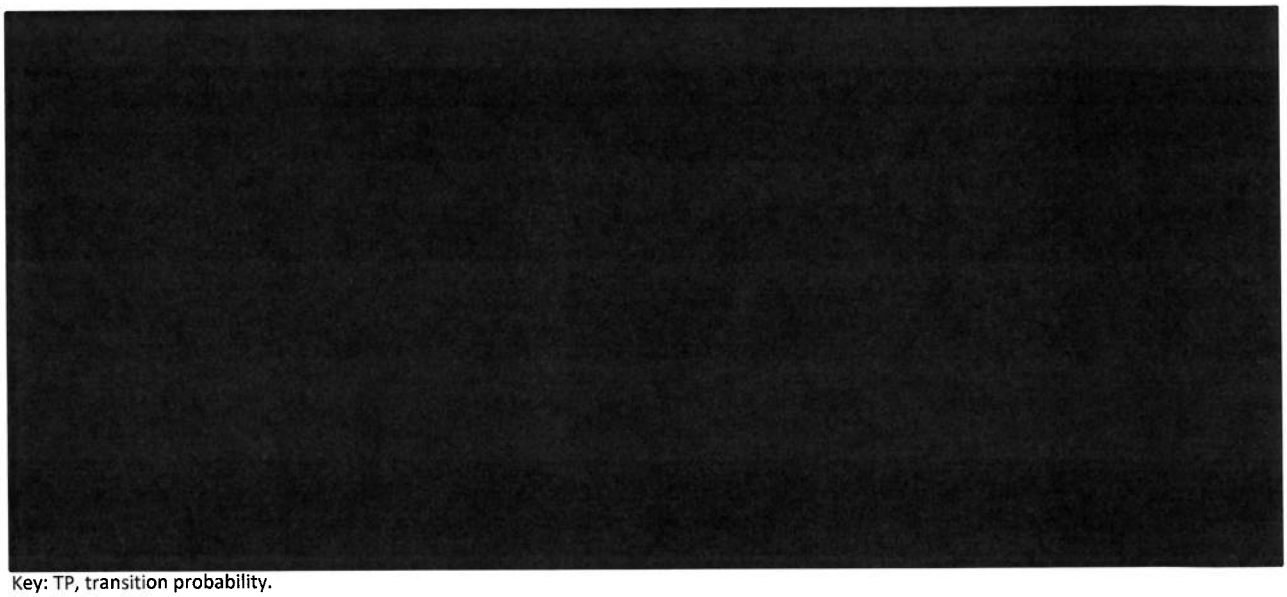
8.7.1 Deterministic sensitivity analyses

Results from the one-way DSAs were plotted in the form of a tornado diagram to visualize the order and the magnitude of the impact of each parameter on different incremental outcomes: incremental costs, incremental LYs, incremental QALYs, and ICER (per QALY or per LY) for dupilumab vs the relevant comparator.

8.7.1.1 Severe allergic asthma subgroup

As dupilumab was dominant in the subgroup, compared to omalizumab + background therapy, a tornado plot is instead presented for incremental cost.

Figure 10. Tornado Diagram (DSA)



Key: TP, transition probability.

The model is most sensitive to the proportion of dupilumab administrations that are either self-managed or managed at an office visit in the adult/adolescent-part of the model (beyond 12 years), and is also sensitive to the unit cost of utensil for subcutaneous administrations.

8.7.1.2 Severe eosinophilic asthma subgroup

As dupilumab was dominant in the subgroup, compared to mepolizumab + background therapy, a tornado plot is instead presented for incremental cost.

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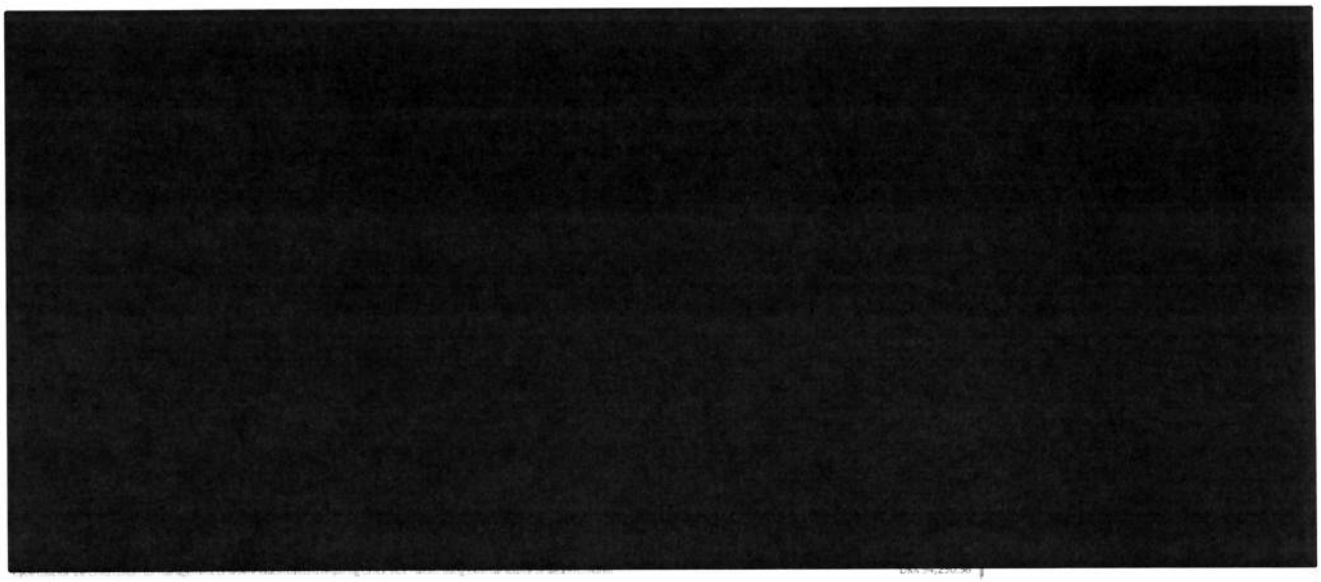
Figure 11. Tornado Diagram (DSA)



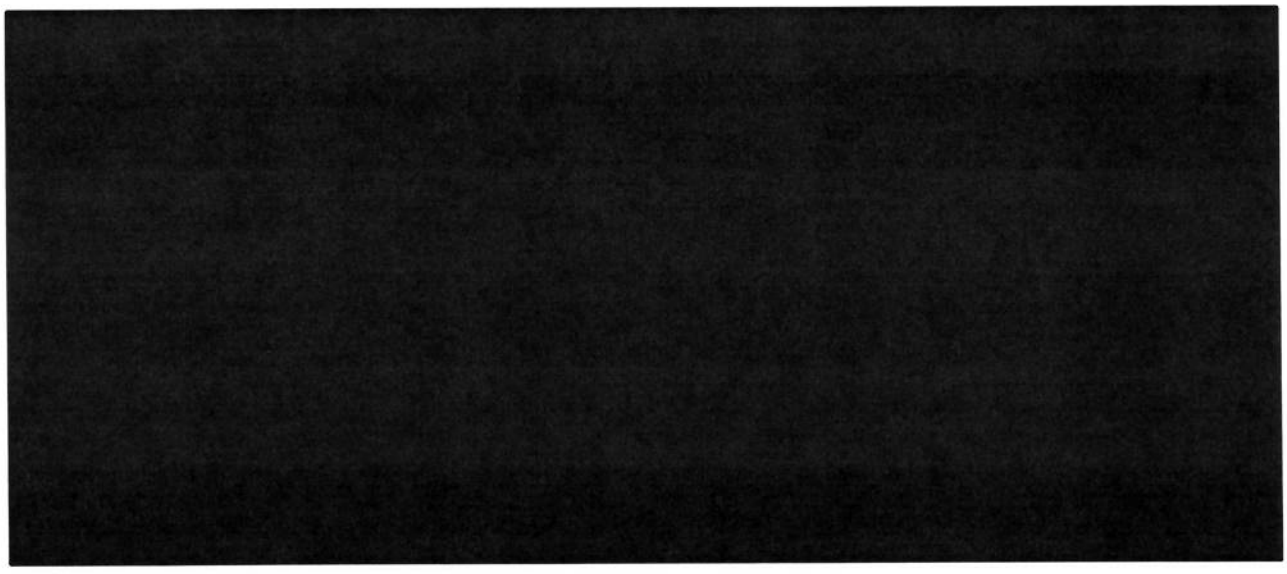
Key: TP, transition probability.

The model is most sensitive to the proportion of mepolizumab administrations that are either self-managed or managed at an office visit in the children population of the model and is also sensitive to the unit cost of utensil for subcutaneous administrations.

8.7.1.3 Severe allergic asthma with elevated FeNO subgroup

A tornado plot is presented for ICER in the comparison between dupilumab vs. background therapy.

Figure 12. Tornado Diagram (DSA)



Key: TP, transition probability.

The model is most sensitive to the proportion of severe exacerbations, that were fatal between 25-34 years, and is also sensitive to the proportion of dupilumab administrations that are either self-managed or managed at an office visit in the adult/adolescent-part of the model (beyond 12 years).

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8.7.2 Probabilistic sensitivity analyses

8.7.2.1 Severe allergic asthma subgroup

The results of the PSA are shown in Figure 13.

Figure 13. Scatter plot for the comparison of dupilumab vs background therapy in the severe allergic asthma subgroup

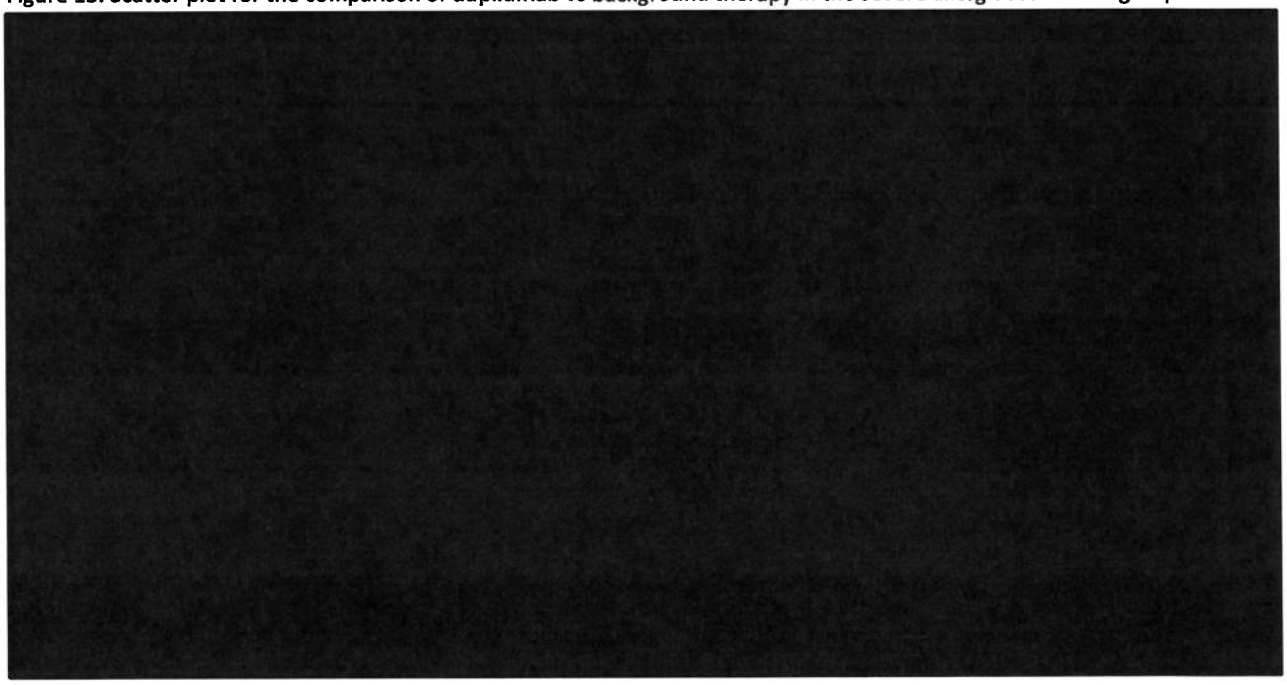

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Figure 14: Cost-effectiveness Acceptability Curve. Probability of dupilumab being the most-effective treatment in the severe allergic asthma subgroup

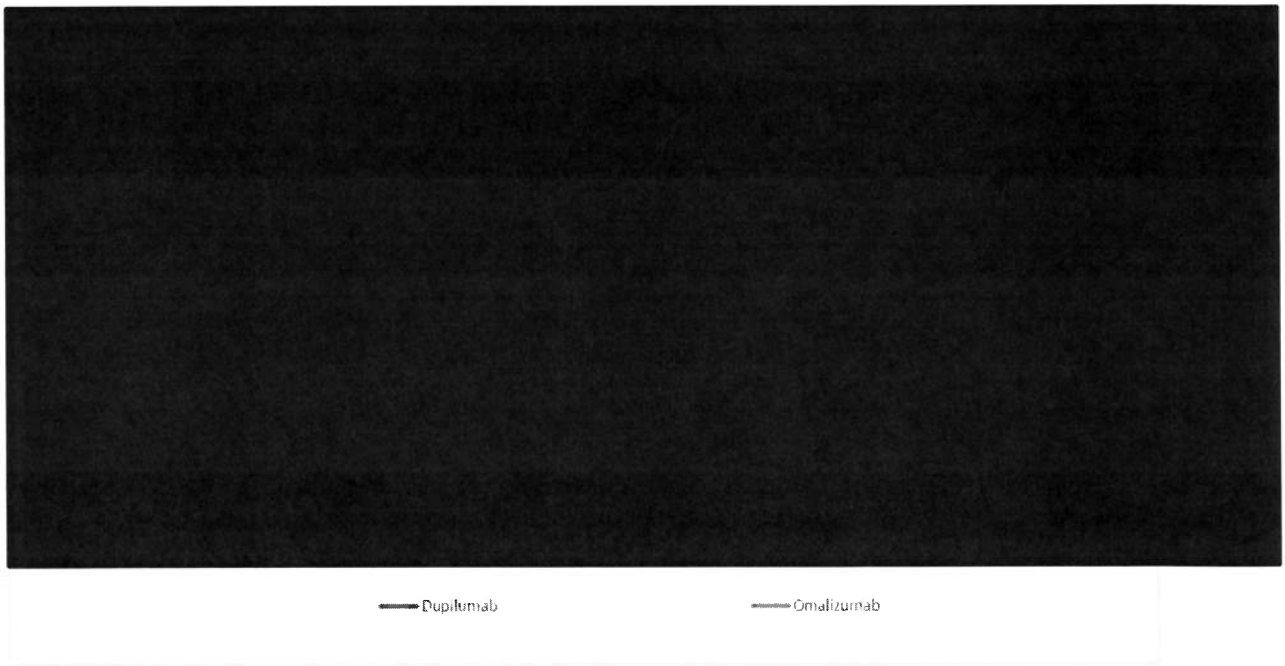

Table 70: Base case cost-effectiveness results for the severe allergic asthma (Probabilistic)

Technology	Total costs (DKK)	Total LYG	Total QALYs	Incremental costs (DKK)	Incremental LYG	Incremental QALYs	ICER vs baseline (DKK/QALY)
Omalizumab + background therapy							
Dupilumab + background therapy							

Table 71. Distribution of iterations in the cost-effectiveness plane (probabilistic) for severe allergic asthma subgroup

Proportion of incremental costs and QALYs falling in:	
North-east quadrant (ICER)	
South-east quadrant (Dominant)	
South-west quadrant (Less costly, less effective)	
North-west quadrant (Dominated)	

The probabilistic mean ICER for children with severe allergic asthma is DKK -4,208,899.53 per QALY, with 66% of the iteration falling with the south-east quadrant (dominant).

8.7.2.2 Severe eosinophilic asthma subgroup

The results of the PSA are shown in Figure 15.

Figure 15. Scatter plot for the comparison of dupilumab vs background therapy in the severe eosinophilic asthma subgroup

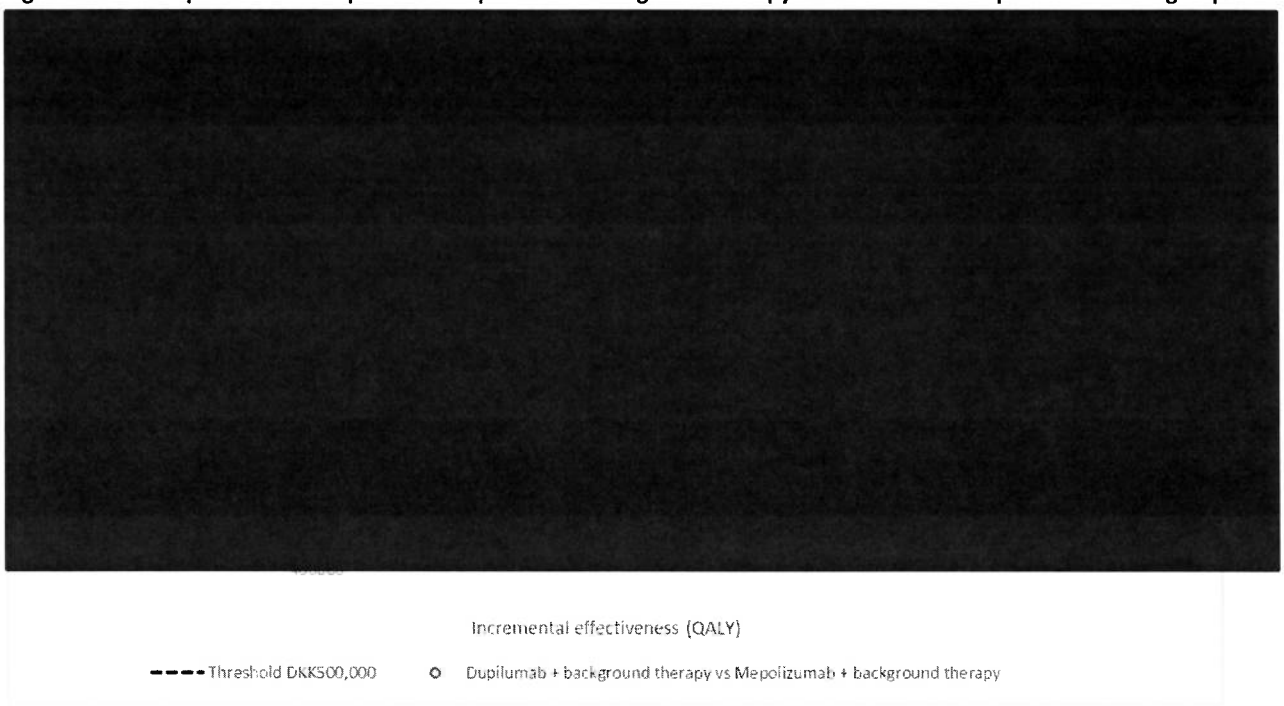

Figure 16. Cost-effectiveness Acceptability Curve. Probability of dupilumab being the most-effective treatment in the severe eosinophilic asthma subgroup

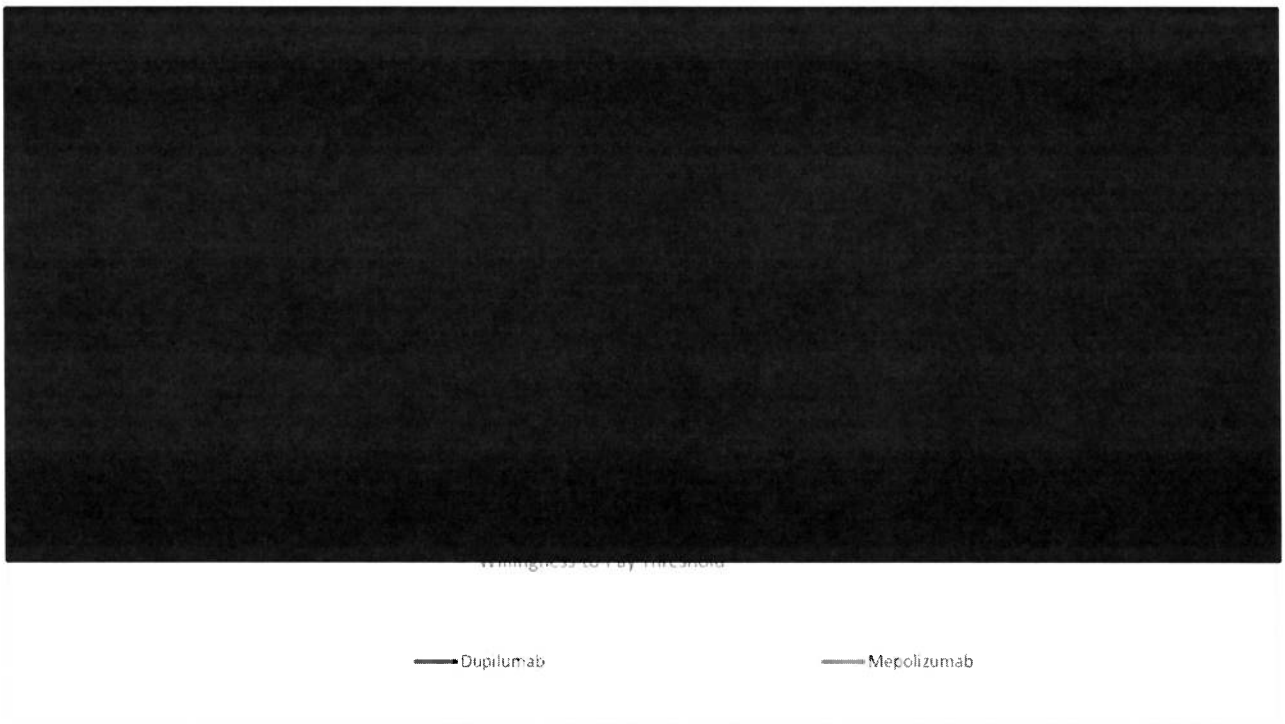

Table 72. Base case cost-effectiveness results for the severe eosinophilic asthma subgroup (Probabilistic)

Technology	Total costs (DKK)	Total LYG	Total QALYs	Incremental costs (DKK)	Incremental LYG	Incremental QALYs	ICER vs baseline (DKK/QALY)
Mepolizumab + background therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Dupilumab + background therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 73. Distribution of iterations in the cost-effectiveness plane (probabilistic) for the severe eosinophilic asthma subgroup

Proportion of incremental costs and QALYs falling in:	
North-east quadrant (ICER)	[redacted]
South-east quadrant (Dominant)	[redacted]
South-west quadrant (Less costly, less effective)	[redacted]
North-west quadrant (Dominated)	[redacted]

The probabilistic ICER for the severe eosinophilic asthma subgroup is DKK -1,218,940 per QALY, with 75% of the iteration fallings in the south-east quadrant (dominant).

8.7.2.3 Severe asthma with elevated FeNO

The results of the PSA are shown in figure (Figure 17)

Figure 17: Scatter plot for the comparison of dupilumab vs background therapy in the severe asthma with elevated FeNO subgroup

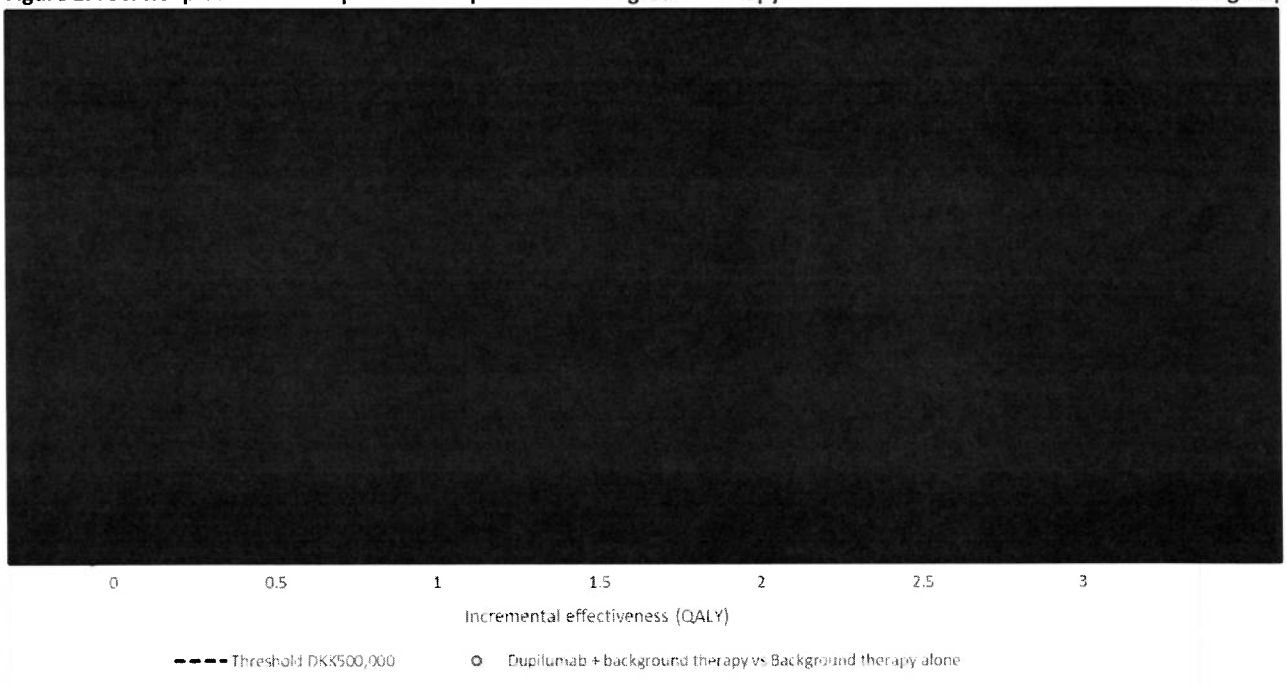

Figure 18: Cost-effectiveness Acceptability Curve. Probability of dupilumab being the most-effective treatment in the severe asthma with elevated FeNO subgroup

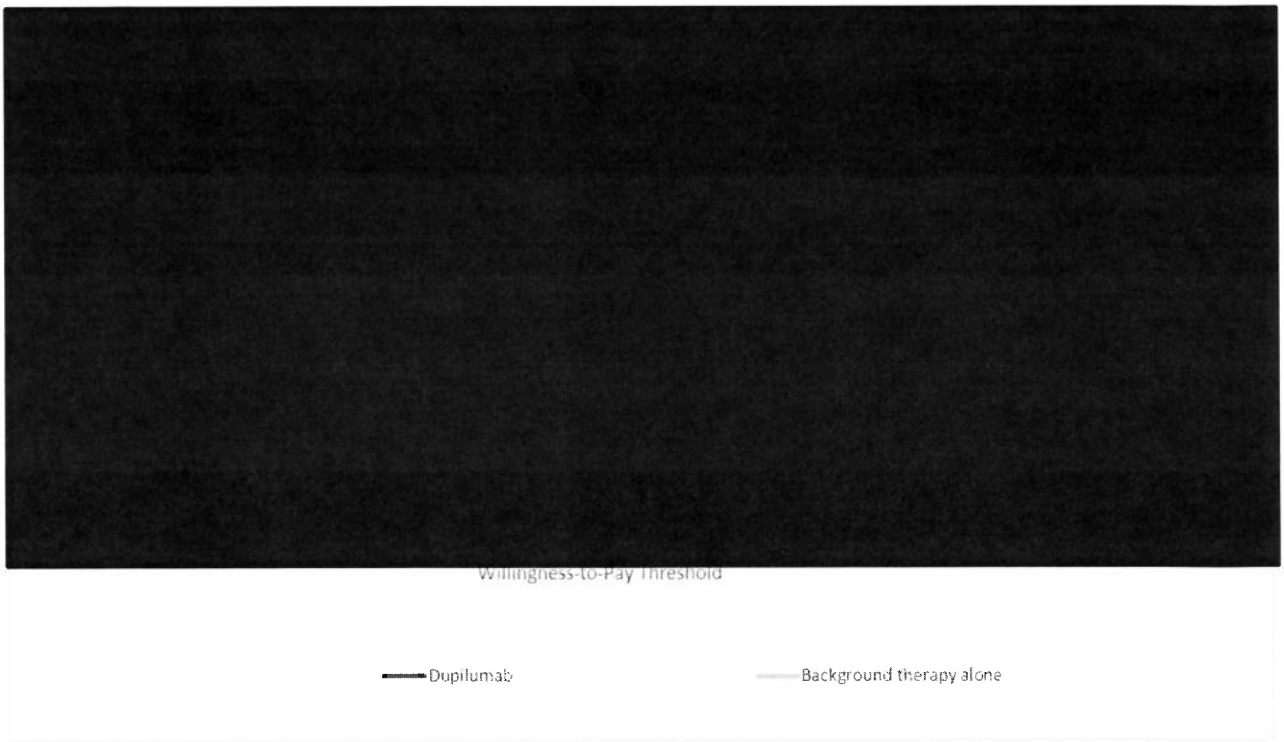

Table 74: Base case cost-effectiveness results for severe asthma with elevated FeNO subgroup

Technology	Total costs (DKK)	Total LYG	Total QALYs	Incremental costs (DKK)	Incremental LYG	Incremental QALYs	ICER vs baseline (DKK/QALY)
Background therapy alone							
Dupilumab + background therapy							

The probabilistic ICER for patients severe asthma with elevated FeNO is DKK 2,160,434 per QALY.

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9. Budget impact analysis

The budget impact model was developed to estimate the expected budget impact of recommending dupilumab as a treatment option in Denmark. The budget impact analysis has been embedded within the cost-effectiveness model and therefore any changes in the settings of the cost per patient model would affect the results of the budget impact model. The budget impact result is representative of the populations in the cost per patient model.

The costs included in the budget impact model are undiscounted, and patient cost and transportation cost have not been included as per the guidelines by the DMC.

The analysis compares the costs for the Danish regions per year over five years in the scenario where dupilumab is recommended as standard treatment and the scenario where dupilumab is not recommended as standard treatment for all three subgroups. The budget impact per year is the difference between the two scenarios.

As the condition is a chronic disease, the budget impact analysis uses an average-based method, as the number of prevalent patients is assumed to be fairly stable across the years, as it is assumed that the number of incident patients would be similar to the number of patients, who exceed the age limit of 11 year of the indication each year.

9.1 Market shares and number of patients

As mentioned in section 5.1.1, using the top-down method approx. 101 paediatric patients with severe asthma are eligible for treatment with dupilumab as add-on to background therapy annually. For ease of calculation, the number of patients has been rounded to **100** patients. [redacted] distribution observed in the Liberty Asthma VOYAGE trial (see Figure 8).

See Table 75 for patient numbers applied in the BIM. These estimates need to be assessed with caution, as numbers are based on the distribution observed in the clinical trial and the definition are not mutually exclusive as described in section 5.1.1 and section 7.3.1. However, to be able to create mutually exclusive subgroups for the BIM, the distributions have been created where subgroup only have been counted once, to avoid any double counting of patients.

Table 75. Number of patients expected to be treated over the next five-year period

	Year 1	Year 2	Year 3	Year 4	Year 5
Total number of patients in total	**100**	**100**	**100**	**100**	**100**
Severe allergic asthma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe eosinophilic asthma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe asthma with elevated FeNO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients out of indication for dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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For the severe allergic asthma subgroup, in the scenarios, where dupilumab is not recommended, dupilumab is not expected to gain any market uptake. In the scenario, where dupilumab is recommended as standard treatment, dupilumab is expected to have slow market uptake, as the existing treatment option is widely used on the Danish market and physicians will have good experience with the treatment (83). Therefore, dupilumab is assumed to achieve 20% market uptake in year 1, which increases to 60% market uptake in year 4. See Table 76.

See Table 76, Table 77 and Table 78 for the tabulated market shares for each subgroup.

Table 76. Market shares over the next five-year period for patients with severe allergic asthma

	Year 1	Year 2	Year 3	Year 4	Year 5
Total number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario where dupilumab is not recommended					
Dupilumab + Background therapy	0%	0%	0%	0%	0%
Omalizumab + background therapy	100%	100%	100%	100%	100%
Scenario where dupilumab is recommended					
Dupilumab + Background therapy	20%	40%	50%	60%	60%
Omalizumab + background therapy	80%	60%	50%	40%	40%

For the severe allergic eosinophilic subgroup, in the scenarios, where dupilumab is not recommended, dupilumab is not expected to gain any market uptake. In the scenario, where dupilumab is recommended as standard treatment, dupilumab is expected to have slow market uptake, as the existing treatment option is widely used on the Danish market and physicians will have good experience with the treatment on the market(83). Therefore, dupilumab is assumed to achieve 20% market uptake in year 1, and due to the stronger data basis for dupilumab, dupilumab is assumed to have a high market uptake in year 5, at 80%. See Table 77.

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Table 77. Market shares over the next five-year period for patients with severe eosinophilic asthma

	Year 1	Year 2	Year 3	Year 4	Year 5
Total number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario where dupilumab is not recommended					
Dupilumab + Background therapy	0%	0%	0%	0%	0%
Mepolizumab + background therapy	100%	100%	100%	100%	100%
Scenario where dupilumab is recommended					
Dupilumab + Background therapy	20%	40%	60%	80%	80%
Mepolizumab + background therapy	80%	60%	40%	20%	20%

For the severe allergic eosinophilic subgroup, in the scenarios, where dupilumab is not recommended, dupilumab is not expected to gain any market uptake. In the scenario, where dupilumab is recommended as standard treatment, dupilumab is expected to gain 100% market share in year 1, as there is no competition on Danish market (83). See Table 78.

Table 78. Market shares over the next five-year period for patients with severe asthma with elevated FeNO

	Year 1	Year 2	Year 3	Year 4	Year 5
Total number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario where dupilumab is not recommended					
Dupilumab + Background therapy	0%	0%	0%	0%	0%
Background therapy alone	100%	100%	100%	100%	100%
Scenario where dupilumab is recommended					
Dupilumab + Background therapy	100%	100%	100%	100%	100%
Background therapy alone	0%	0%	0%	0%	0%

9.2 Budget impact result

9.2.1 Severe allergic asthma

Based on the base case settings, the estimated budget impact of recommending dupilumab as standard treatment for patients with severe allergic asthma in Denmark at PPP is approx. DKK -136,772 in year 1 and approx. DKK -410,316 in year 5 as shown in Table 79.

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Table 79. Expected budget impact of recommending dupilumab as standard treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
Without recommendation	DKK 6,017,432	DKK 6,017,432	DKK 6,017,432	DKK 6,017,432	DKK 6,017,432
With recommendation	DKK 5,880,660	DKK 5,743,888	DKK 5,675,502	DKK 5,607,116	DKK 5,607,116
Budget impact of the recommendation	**DKK -136,772**	**DKK -273,544**	**DKK -341,930**	**DKK -410,316**	**DKK -410,316**

9.2.2 Severe eosinophilic asthma

Based on the base case settings, the estimated budget impact of recommending dupilumab as standard treatment for patients with severe eosinophilic asthma in Denmark at PPP is approx. DKK -89,087 in year 1 and approx. DKK -356,347 in year 5 as shown in Table 80.

Table 80. Expected budget impact of recommending dupilumab as standard treatment for patients with severe eosinophilic asthma

	Year 1	Year 2	Year 3	Year 4	Year 5
Without recommendation	DKK 1,878,032	DKK 1,878,032	DKK 1,878,032	DKK 1,878,032	DKK 1,878,032
With recommendation	DKK 1,788,945	DKK 1,699,858	DKK 1,610,772	DKK 1,521,685	DKK 1,521,685
Budget impact of the recommendation	**DKK -89,087**	**DKK -178,173**	**DKK -267,260**	**DKK -356,347**	**DKK -356,347**

9.2.3 Severe asthma with elevated FeNO

Based on the base case settings, the estimated budget impact of recommending dupilumab as standard treatment for patients with severe allergic asthma in Denmark at PPP is approx. DKK 178,430 every year as shown in Table 81.

Table 81: Expected budget impact of recommending dupilumab as standard treatment for patients with severe asthma with elevated FeNO

	Year 1	Year 2	Year 3	Year 4	Year 5
Without recommendation	DKK 59,223	DKK 59,223	DKK 59,223	DKK 59,223	DKK 59,223
With recommendation	DKK 237,654	DKK 237,654	DKK 237,654	DKK 237,654	DKK 237,654
Budget impact of the recommendation	**DKK 178,430**	**DKK 178,430**	**DKK 178,430**	**DKK 178,430**	**DKK 178,430**

10. Discussion on the submitted documentation

10.1 Heterogeneity in clinical comparisons

The heterogeneity with respect to study design, inclusion criteria, outcomes definition, and the lack of reporting of key baseline characteristics presented barriers in terms of the comparability of studies.

Patients in the VOYAGE trial(24) were broadly defined as those with uncontrolled moderate-to-severe asthma for more than one year while on a medium dose ICS in combination with a second controller, high dose ICS alone, or high dose ICS in combination with a second controller. On the other hand, the omalizumab trials(3, 5, 15, 92, 93) included patients with moderate-to-severe allergic asthma who were inadequately controlled despite at least medium dose ICS or who had persistent disease that was uncontrolled for more than one year. The mepolizumab trial(18) included patients with severe asthma with an eosinophilic phenotype.

The ITT population of VOYAGE trial had no inclusion criteria with regards to specific biomarkers, but the primary populations of interest were defined by biomarkers (i.e., Type 2 asthma: EOS ≥150 cells per cubic millimeter or a FeNO of ≥20 ppb at baseline or high EOS: EOS≥300 cells per cubic millimeter). In comparison, the omalizumab trials had the inclusion requirement of IgE levels ranging from 30 to 1300 IU/mL. There was also a high degree of heterogeneity across the included trials with regards to baseline patient characteristics such as age, study region/race, EOS, ppFEV1, IgE, and higher number of prior exacerbations. These differences need to be considered in the context of the observed outcomes, since omalizumab and mepolizumab were studied in narrower patient populations than studied in VOYAGE; allergic phenotype and eosinophilic phenotypes, respectively.

10.2 Uncertainty in clinical comparisons

In order to provide comparable results, subgroup analyses were conducted to align with the subgroup definitions of the adult/adolescent treatment guideline for severe asthma, and therefore allowing for a better basis of comparison with the omalizumab trial and the mepolizumab trial. This partially breaks randomization and reduces in sample size of the data from the VOYAGE trial.

However, as few endpoints were comparable in the comparison between VOYAGE and the omalizumab trial (IA05), it was not possible to conduct ITC using methods such as, a Bucher's ITC or a matching adjusted indirect comparison. For this comparison, efficacy and safety were instead compared through a narrative synthesis. It was therefore not possible to conclude whether dupilumab was a superior treatment when compared to omalizumab in the severe allergic asthma subgroup.

In the dupilumab comparison versus mepolizumab, several limitations pertained the limited data of the mepolizumab trial, both in terms of study population, trial design and endpoints presented. The mepolizumab trial was a non-randomised, open-label, repeat-dose phase II-trial, which included 36 paediatric patients. The trial did not provide any data on exacerbations, hence not making a comparison on these endpoints possible. In the cases, where data was presented for mepolizumab, the small samples size did not constitute a strong basis for a credible conclusion. It did appear that dupilumab potentially could be a superior treatment compared to mepolizumab, however, when the limited data set for mepolizumab, it was not possible to draw any definitive conclusion from this comparison.

10.3 Health economic interpretation

The health economic analysis demonstrated that dupilumab was dominant in the severe allergic asthma subgroup (versus omalizumab) and dominant in the severe eosinophilic asthma subgroup (versus mepolizumab), while an ICER of approx. 2 mil. DKK per QALY was estimated for dupilumab compared to placebo in the severe asthma with elevated FeNO subgroup where dupiliumab was compared to placebo.

In the VOYAGE trial, HRQoL was captured using the EQ-5D-Y questionnaire. This provided a limitation, as no Danish value have been published for EQ-5D-Y to support its use in economic evaluation, furthermore the EuroQol group have advised against the use of EQ-5D-3L value sets as proxy sets for the EQ-5D-Y questionnaire. However, in the absence of a better option to derive EQ-5D-Y score in children, the Danish EQ-5D-3L value set have been used in the base-case to derive utilities for the children population. This further introduces uncertainty to the analysis, as it is most unlikely that children would value the domains in the questionnaire equally as adults. Furthermore, the EQ-5D-Y questionnaire's domains have been altered to more appropriate for children and does not align with the domains in the adult EQ-5D-3L and EQ-5D-5L questionnaire. Therefore, for the base-case to reduce the number of steps in order to derive utility values for the child-population, the Danish EQ-5D-3L value set have been used instead of a reverse-crosswalk EQ-5D-5L value set.

For the health economic analysis, **exploratory ITCs have been conducted for the comparison between dupilumab and omalizumab for severe exacerbations,** despite the difference in study design, patient population and the definition of severe exacerbations. The analyses were conducted in order to provide a basis for comparison between dupilumab and omalizumab, and to demonstrate the relative efficacy differences. The analyses are of an exploratory nature, and therefore the clinical assessments could not be based on the conducted ITC, due to the uncertainty pertaining to the differences between the trials. It is possible to remove the effect of the exploratory ITC within the model.

For the comparison with mepolizumab, it was not possible to conduct any ITCs on severe exacerbations. Therefore, data input from the adult/adolescent population was assumed to be applicable for the child population. However, as no strong data for mepolizumabs efficacy in children is available, it was not possible to confirm the likelihood of this assumption to be correct. This is therefore a limitation in the comparison with mepolizumab in the severe eosinophilic asthma subgroup in the health economic analysis.

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148. Dewilde S, Turk F, Tambour M, Sandstrom T. The economic value of anti-IgE in severe persistent, IgE-mediated (allergic) asthma patients: adaptation of INNOVATE to Sweden. Curr Med Res Opin. 2006;22(9):1765-76.
149. Suzuki C LdSN, Kumar P, Pathak P, Ong SH. Cost-effectiveness of omalizumab add-on to standard-of-care therapy in patients with uncontrolled severe allergic asthma in a Brazilian healthcare setting. Journal of medical economics. 2017;20(8):832-9.
150. Willson J, Bateman ED, Pavord I, Lloyd A, Krivasi T, Esser D. Cost effectiveness of tiotropium in patients with asthma poorly controlled on inhaled glucocorticosteroids and long-acting β-agonists. Appl Health Econ Health Policy. 2014;12(4):447-59.
151. Dal Negro RW, Tognella S, Pradelli L. A 36-month study on the cost/utility of add-on omalizumab in persistent difficult-to-treat atopic asthma in Italy. The Journal of asthma : official journal of the Association for the Care of Asthma. 2012;49(8):843-8.
152. Faria R, McKenna C, Palmer S. Optimizing the position and use of omalizumab for severe persistent allergic asthma using cost-effectiveness analysis. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2014;17(8):772-82.
153. Whittington MD, McQueen RB, Chapman RH, Tice JA, Ollendorf D, Campbell JD. Cost Effectiveness Of Mepolizumab In Adult Asthma Patients. Value in Health.19(3):A116.

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154. Zein JG, Menegay MC, Singer ME, Erzurum SC, Gildea TR, Cicenia JC, et al. Cost effectiveness of bronchial thermoplasty in patients with severe uncontrolled asthma. The Journal of asthma : official journal of the Association for the Care of Asthma. 2016;53(2):194-200.

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Appendix A Literature search for efficacy and safety of intervention and comparator(s)

SLR Methods

Standard methods for conducting and reporting an SLR were used per the Cochrane Handbook(20, 21) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines(22, 23) to satisfy the requirements of the National Institute for Health Care Excellence (NICE).

Identification and Selection of Relevant Studies

Search strategy

Systematic literature searches were conducted in Embase, MEDLINE, and the Cochrane Central Register of Controlled Clinical Trials via Ovid (http://ovidsp.ovid.com/) to identify studies of interest. The strategies for each electronic literature database included a combination of free-text and medical subject headings, grouped into the following categories: population, interventions, study design, and limits (including timeframe, language, and publication type). Searches were restricted to studies conducted in humans and published in English. The searches spanned from 1998 (pre-dating the earliest published omalizumab trial in paediatric asthma(94)) to February 2021 for full-text publications.

Table 82. Electronic Literature Databases

Topic	Electronic Literature Databases
Electronic databases	Embase via Ovid
	MEDLINE via Ovid
	CENTRAL via Ovid

Abbreviation: CENTRAL = Cochrane Central Register of Controlled Trials

Gray literature searches (January 2019 to February 2021) were conducted to identify recent relevant research that may not have been published in peer-reviewed journals. Conference proceedings from the following five key conferences were searched:

- American Academy of Allergy, Asthma, and Immunology (AAAAI)
- American Thoracic Society (ATS)
- British Thoracic Society (BTS)
- European Academy of Allergy and Clinical Immunology (EAACI)
- European Respiratory Society (ERS)

The bibliographies of relevant SLRs identified across the electronic database searches were screened to check for any additional relevant references. Furthermore, the clinical trial registry of ClinicalTrials.gov was also reviewed to identify any ongoing trials conducted in the target population of interest.

Searches were run in all databases of interest as specified. After de-duplication, the search results were exported to an EndNote® library and uploaded to Distiller Systematic Review software, an internet-based program that facilitates the selection process in a transparent manner.

12.1.1 Study Selection

Studies were screened and selected for inclusion in the SLR based on the populations, interventions, comparators, outcomes, study design, and timeframe criteria (PICOS-T), as displayed in Table 83. Screening questions were developed based on these criteria. Prior to the formal screening process, the researchers tested the questions via pilot screening

and refined them to ensure appropriateness for use. The screening process involved the following stages: dual screening conducted by two independent investigators with any discrepancies resolved by a third investigator.

Table 83. Eligibility Criteria Used in the Search Strategy

PICOS-T	Inclusion Criteria	Exclusion Criteria
Population	Paediatric patients age 6 to <12 years with uncontrolled, moderate-to-severe asthma *Studies conducted in mixed age populations will be included if subgroup data are reported for ages of interest, if ≥80%* of the included patients are within the age group of interest, or if the mean/median age is <12 years* Subgroups of interest: Type 2 inflammation, EOS≥300, EOS≥150, FeNO≥20	Patients ages <6 and ≥12 years old (studies including patients <6 years of age will be tagged during screening) Patients with mild asthma Patients with acute asthma
Interventions	Approved, recommended, or emerging biologic treatments administered as add-on to SOC including, but not limited to: Dupilumab Mepolizumab Omalizumab Benralizumab Reslizumab	Studies that evaluate treatment other than those listed as interventions of interest in the inclusion criteria
Comparators	Any (including placebo, SOC, and OAT) or none for single-arm trials	NA
Outcomes	Efficacy Severe exacerbations (annualized rate, time to first) resulting in hospitalization or emergency room visit, or study defined) Change in % predicted pre-bronchodilator FEV_1 Change in other lung function parameters (absolute pre-bronchodilator FEV_1, FVC, $FEF_{25\%-75\%}$, FEV_1/FVC ratio, morning and evening PEF) Annualized rate of LOAC Systemic corticosteroid use Asthma symptom score (morning and evening) Nocturnal awakenings Rescue medication use Change in FeNO PROs Changes in ACQ scores (includes ACQ-5 and ACQ-7) Changes in PAQLQ scores EQ-5D-Y PRQLQ-IA	Studies that do not report at least one of the outcomes of interest listed in the inclusion criteria

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	PACQLQ Safety Total (any grade) AEs Total severe/serious AEs Treatment-emergent/related AEs Treatment-emergent SAE All-cause mortality Drug discontinuations due to any reason Study or drug discontinuations due to AEs/TEAE injection site reactions	
Study design	Phase II, III, and IV clinical trials, including: RCTs (including cross-over designs) Open-label trials (including long-term extensions) Single-arm trials Pooled analysis of eligible trials	Observational studies Phase I clinical trials Pre-clinical studies (animal, in vitro) Case reports, expert opinion articles, editorials, letters, narrative (non-systematic reviews) Articles or conference abstracts published in languages other than English SLRs published in the last five years will be used for citation chasing but not extracted and included within the review
Time Period	1998 through February 2021 for full-text publications 2019 through February 2021 for gray literature	Studies published after February 2021
Language†	English	Languages other than English

*Studies in which the inclusion criterion for the study population is fulfilled in less than 80% of the patients included in the study will be excluded, as suggested appropriate in the SLR guidelines for the Institute for Quality and Efficiency in Health Care(95)

†Non-English studies will be tagged, in particular for countries of interest defined by the economic literature reviews for EVG-29717 (United States, Canada, United Kingdom, Norway, Sweden, Italy, Germany, Spain, Denmark, France, and Australia)

Abbreviations: ACQ = Asthma Control Questionnaire; AE = adverse event; EOS = eosinophil; FEF = forced expiratory flow; FeNO = fraction of exhaled nitric oxide; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; LOAC = loss of asthma control; NA = not applicable; OAT = optimized asthma therapy; PACQLQ = **Pediatric Asthma Caregiver's Quality of Life Questionnaire;** PAQLQ = Pediatric Asthma Quality of Life Questionnaire; PEF = peak expiratory flow; PICOS-T = populations, interventions, comparators, outcomes, study design, and timeframe; PRO = patient-reported outcome; PRQLQ = **Pediatric Rhinoconjunctivitis Quality of Life Questionnaire**; RCT = randomized controlled trial; SAE = serious adverse event; SLR = systematic literature review; SOC = standard of care; TEAE = treatment-emergent adverse event

12.2 Embase Search via Ovid

Table 84. Embase Search Strategy

Search Number	Embase Search Terms	Results (1/28/2021)
1	exp asthma/ or (asthma or asthmatic or anti-asthmatic or antiasthmatic).ti,ab.	298074
2	(Type 2 or Moderate or Severe or Moderate-to-severe or Persistent or partially control$ or uncontrol$ or inadequate control$ or inadequately control$ or severe uncontrol$ or difficult to treat).ti,ab.	2524584

3	(gina-3 or gina-4 or gina-5).ti,ab.	66
4	((gina adj2 '3') or (gina adj2 '4') or (gina adj2 '5') or (gina adj2 '4-5') or (gina adj2 '3-5')).ti,ab.	269
5	2 or 3 or 4	2524615
6	1 and 5	59067
7	dupilumab/ or (dupilumab or SAR231893 or SAR231893 or REGN-668 or REGN668).ti,ab.	2310
8	omalizumab/ or (omalizumab or Xolair or GN-1560 or GN1560).ti,ab.	8877
9	mepolizumab/ or (mepolizumab or Nucala or SB-240563 or SB240563).ti,ab.	2982
10	reslizumab/ or (Reslizumab or s.c.H-55700 or s.c.H55700 or CEP-38072 or CEP38072 or DCP-835 or DCP835 or Cinqair).ti,ab.	1123
11	benralizumab/ or (benralizumab or BIW-8405 or BIW8405 or KHK-4563 or KHK4563 or MEDI-563 or MEDI563 or fasenra).ti,ab.	1168
12	interleukin 4/ad, an, cb, cm, cr, dv, do, it, dt, to or (anti-il-4 or anti-il4 or anti-interleukin-4 or ((interleukin-4 or IL-4 or IL4) adj2 (antagonist$ or inhibit$ or block$))).ti,ab.	4943
13	interleukin 5/ad, an, cb, cm, cr, dv, do, it, dt, to or (anti-il-5 or anti-il5 or anti-interleukin-5 or ((interleukin-5 or IL-5 or IL5) adj2 (antagonist$ or inhibit$ or block$))).ti,ab.	2032
14	interleukin 13/ad, an, cb, cm, cr, dv, do, it, dt, to or (anti-il-13 or anti-il13 or anti-interleukin-13 or ((interleukin-13 or IL-13 or IL13) adj2 (antagonist$ or inhibit$ or block$))).ti,ab.	1489
15	or/7-14	19446
16	6 and 15	5075
17	Clinical Trial/	998359
18	Randomized Controlled Trial/	641839
19	controlled clinical trial/	466048
20	multicenter study/	276038
21	Phase 3 clinical trial/	51039
22	Phase 4 clinical trial/	4159
23	exp RANDOMIZATION/	90076
24	Single Blind Procedure/	41600
25	Double Blind Procedure/	180632
26	Crossover Procedure/	65906
27	PLACEBO/	361846
28	randomi?ed controlled trial$.tw.	248620
29	rct.tw.	40479
30	(random$ adj2 allocat$).tw.	45568
31	single blind$.tw.	26349

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32	Double blind$.tw.	217065
33	((treble or triple) adj blind$).tw.	1288
34	placebo$.tw.	320726
35	Prospective Study/	657355
36	(single arm trial or singl* or single-arm).tw.	2192623
37	(post-hoc or posthoc).tw.	63452
38	or/17-37	4412825
39	Case Study/	75475
40	case report.tw.	437294
41	abstract report/ or letter/	1184719
42	Conference proceeding.pt.	0
43	Editorial.pt.	682496
44	Letter.pt.	1160488
45	Note.pt.	836140
46	or/39-45	3271552
47	38 not 46	4248023
48	16 and 47	2001
49	48 not ((exp animal/ or nonhuman/) not exp human/)	1981
50	limit 49 to (article or article in press)	608
51	49 and (systematic or (meta and analy$) or ((indirect or mixed) and treatment comparison)).ti,ab.	136
52	eaaci.cf,cg.	6950
53	ats.cf,cg.	55224
54	european respiratory society.cf,cg.	38974
55	AAAAI.cf,cg.	11573
56	british thoracic society.cf,cg.	4835
57	or/52-56	117556
58	49 and 57	572
59	limit 58 to yr="2019 -Current"	182
60	50 or 51 or 59	865
61	limit 60 to yr="1998 -Current"	864

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12.3 MEDLINE Search via Ovid

Table 85. MEDLINE Search Strategy

Search Number	MEDLINE Search Terms	Results (1/28/2021)
1	exp asthma/ or (asthma or asthmatic or anti-asthmatic or antiasthmatic).ti,ab.	181665
2	(Type 2 or Moderate or Severe or Moderate-to-severe or Persistent or partially control$ or uncontrol$ or inadequate control$ or inadequately control$ or severe uncontrol$ or difficult to treat).ti,ab.	1782749
3	(gina-3 or gina-4 or gina-5).ti,ab.	16
4	((gina adj2 '3') or (gina adj2 '4') or (gina adj2 '5') or (gina adj2 '4-5') or (gina adj2 '3-5')).ti,ab.	67
5	2 or 3 or 4	1782758
6	1 and 5	31377
7	dupilumab/ or (dupilumab or dupixent or SAR231893 or SAR231893 or REGN-668 or REGN668).ti,ab.	861
8	omalizumab/ or (omalizumab or Xolair or GN-1560 or GN1560).ti,ab.	2717
9	mepolizumab/ or (mepolizumab or Nucala or SB-240563 or SB240563).ti,ab.	670
10	reslizumab/ or (Reslizumab or s.c.H-55700 or s.c.H55700 or CEP-38072 or CEP38072 or DCP-835 or DCP835 or Cinqair).ti,ab.	230
11	benralizumab/ or (benralizumab or BIW-8405 or BIW8405 or KHK-4563 or KHK4563 or MEDI-563 or MEDI563 or fasenra).ti,ab.	315
12	Interleukin-4/ai or (anti-il-4 or anti-il4 or anti-interleukin-4 or ((interleukin-4 or IL-4 or IL4) adj2 (antagonist$ or inhibit$ or block$))).ti,ab.	2944
13	Interleukin-5/ai or (anti-il-5 or anti-il5 or anti-interleukin-5 or ((interleukin-5 or IL-5 or IL5) adj2 (antagonist$ or inhibit$ or block$))).ti,ab.	1340
14	Interleukin-13/ai or (anti-il-13 or anti-il13 or anti-interleukin-13 or ((interleukin-13 or IL-13 or IL13) adj2 (antagonist$ or inhibit$ or block$))).ti,ab.	933
15	or/7-14	8527
16	6 and 15	1800
17	Randomized Controlled Trials as Topic/	139949
18	randomized controlled trial/	521594
19	Random Allocation/	104516
20	Double Blind Method/	162036
21	Single Blind Method/	29632
22	clinical trial/	527122
23	clinical trial, phase i.pt.	21180
24	clinical trial, phase ii.pt.	34076

25	clinical trial, phase iii.pt.	17801
26	clinical trial, phase iv.pt.	2033
27	controlled clinical trial.pt.	94042
28	randomized controlled trial.pt.	521594
29	multicenter study.pt.	287060
30	clinical trial.pt.	527122
31	exp Clinical Trials as topic/	351583
32	or/17-31	1404926
33	(clinical adj trial$).tw.	390378
34	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	178087
35	PLACEBOS/	35312
36	placebo$.tw.	222536
37	randomly allocated.tw.	30383
38	(allocated adj2 random$).tw.	33779
39	(single arm trial or singl* or single-arm).tw.	1745812
40	(post-hoc or posthoc).tw.	35776
41	or/33-40	2359410
42	32 or 41	3296264
43	case report.tw.	327664
44	letter/	1122054
45	historical article/	361878
46	or/43-45	1795063
47	42 not 46	3238320
48	16 and 47	703
49	48 not (animals/ not humans/)	702
50	limit 49 to yr="1998 -Current"	702

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12.4 Cochrane Central Register of Controlled Trials via Ovid

Table 86. Cochrane Search Strategy

Search Number	CENTRAL Search Terms	Results (1/28/2021)
1	exp asthma/ or (asthma or asthmatic or anti-asthmatic or antiasthmatic).ti,ab.	33177
2	(Type 2 or Moderate or Severe or Moderate-to-severe or Persistent or partially control$ or uncontrol$ or inadequate control$ or inadequately control$ or severe uncontrol$ or difficult to treat).ti,ab.	233341
3	(gina-3 or gina-4 or gina-5).ti,ab.	17
4	((gina adj2 '3') or (gina adj2 '4') or (gina adj2 '5') or (gina adj2 '4-5') or (gina adj2 '3-5')).ti,ab.	94
5	2 or 3 or 4	233366
6	1 and 5	10589
7	dupilumab/ or (dupilumab or dupixent or SAR231893 or SAR231893 or REGN-668 or REGN668).ti,ab.	437
8	omalizumab/ or (omalizumab or Xolair or GN-1560 or GN1560).ti,ab.	963
9	mepolizumab/ or (mepolizumab or Nucala or SB-240563 or SB240563).ti,ab.	312
10	reslizumab/ or (Reslizumab or s.c.H-55700 or s.c.H55700 or CEP-38072 or CEP38072 or DCP-835 or DCP835 or Cinqair).ti,ab.	141
11	benralizumab/ or (benralizumab or BIW-8405 or BIW8405 or KHK-4563 or KHK4563 or MEDI-563 or MEDI563 or fasenra).ti,ab.	208
12	Interleukin-4/ai or (anti-il-4 or anti-il4 or anti-interleukin-4 or ((interleukin-4 or IL-4 or IL4) adj2 (antagonist$ or inhibit$ or block$))).ti,ab.	176
13	Interleukin-5/ai or (anti-il-5 or anti-il5 or anti-interleukin-5 or ((interleukin-5 or IL-5 or IL5) adj2 (antagonist$ or inhibit$ or block$))).ti,ab.	199
14	Interleukin-13/ai or (anti-il-13 or anti-il13 or anti-interleukin-13 or ((interleukin-13 or IL-13 or IL13) adj2 (antagonist$ or inhibit$ or block$))).ti,ab.	122
15	or/7-14	2156
16	6 and 15	988
17	Randomized Controlled Trials as Topic/	5966
18	randomized controlled trial/	131
19	Random Allocation/	20647
20	Double Blind Method/	139504
21	Single Blind Method/	21263
22	clinical trial/	33
23	clinical trial, phase i.pt.	5375
24	clinical trial, phase ii.pt.	11888

25	clinical trial, phase iii.pt.	15004
26	clinical trial, phase iv.pt.	1089
27	controlled clinical trial.pt.	91833
28	randomized controlled trial.pt.	508588
29	multicenter study.pt.	89362
30	clinical trial.pt.	280013
31	exp Clinical Trials as topic/	42392
32	or/17-31	597903
33	(clinical adj trial$).tw.	183109
34	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	282947
35	PLACEBOS/	24123
36	placebo$.tw.	311518
37	randomly allocated.tw.	37716
38	(allocated adj2 random$).tw.	42654
39	(single arm trial or singl* or single-arm).tw.	182693
40	(post-hoc or posthoc).tw.	20593
41	or/33-40	673350
42	32 or 41	998096
43	case report.tw.	2272
44	letter/	0
45	historical article/	0
46	or/43-45	2272
47	42 not 46	996805
48	16 and 47	749
49	48 not (animals/ not humans/)	749
50	limit 49 to yr="1998 -Current"	749

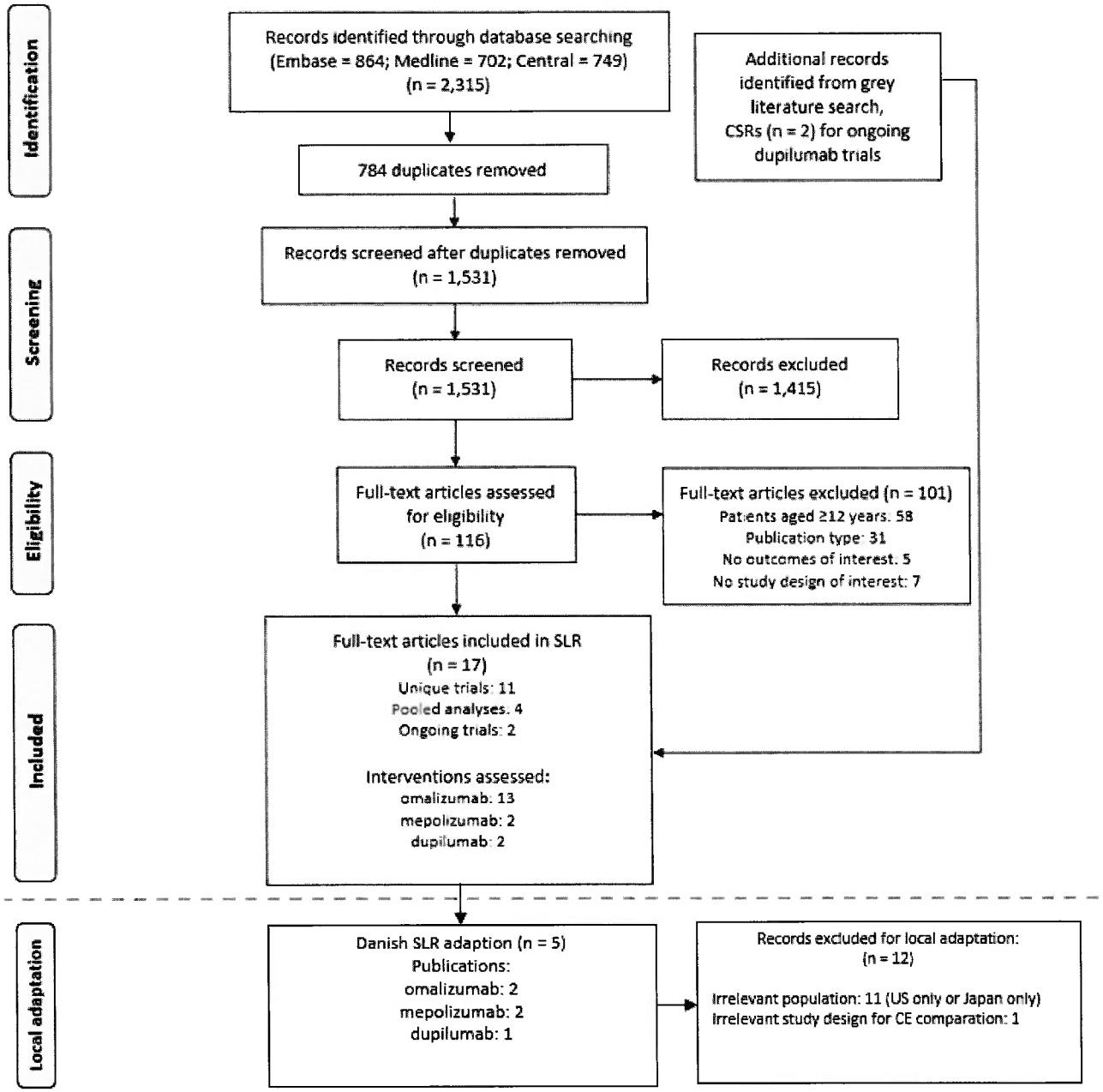
Systematic selection of studies

The literature searches identified 2,315 records from the electronic databases and two from grey literature sources. Of those, 116 abstracts were accepted for further review in full text. Ultimately, 17 publications reporting on seven unique trials(3, 5, 15, 18, 92, 93, 96) and two open-label extension (OLE) studies(97, 98) met the eligibility criteria for inclusion in the global SLR. Full details on the study attrition through the abstract and full-text levels of screening, including reasons for exclusion at the full-text level, are shown in Figure 19. The treatments of interest investigated across the eligible

studies included approved or recommended biologics consisting of dupilumab (two publications on one trial and one OLE), omalizumab (13 publications on five trials and one OLE), and mepolizumab (two publications on one trial). Two ongoing trials (MUPPITS-2(99) and TATE(100)) were identified via clinical trial registries evaluating mepolizumab and benralizumab, respectively. However, neither provided published results at the time of review, and therefore are not detailed in this version of the report.

For the local adaptation of the SLR, 11 populations were excluded due to irrelevant study populations (only US or Japanese patients) and 1 populations was excluded, as it was not deemed relevant for the CE comparison. The studies based on US and Japanese-only populations have been excluded as these populations are unlikely to reflect the Danish population in scope due to differences in ethnicity.

Figure 19. PRISMA Diagram



List of excluded studies with reason:

EVG-29320_Dupilumab%20Pediatric%20A

List of included studies:

Table 87. Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
Dupilumab in Children with Uncontrolled Moderate-to-Severe Asthma, L.B. Bacharier, J.F. Maspero, C.H. Katelaris, A.G. Fiocchi, R. Gagnon, I. de Mir, N. Jain, L.D. Sher, X. Mao, D. Liu, Y. Zhang, A.H. Khan, U. Kapoor, F.A. Khokhar, P.J. Rowe, Y. Deniz, M. Ruddy, E. Laws, N. Patel, D.M. Weinreich, G.D. Yancopoulos, N. Amin, L.P. Mannent, D.J. Lederer, and M. Hardin, N Engl J Med, 2021	Liberty Asthma VOYAGE	NCT02948959	April 21, 2017 – August 26, 2020	Dupilumab vs. Placebo for children with uncontrolled moderate-to-severe asthma
Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma, B. Lanier, T. Bridhes, M. Kulus, A.F. Taylor, I. Berhane, C.F. Vidaurre, J Allergy Clin Immunol, 2009	IA05	NCT00079937	April 2004 – March 2008	Omalizumab vs. Placebo for children with moderate-to-severe, persistent, inadequately controlled allergic asthma
Omalizumab in children with inadequately controlled severe allergic (IgE-mediated) asthma, M. Kulus, J. Hébert, E. Garcia, C.F. Vidaurre, M. Blogg, Curr Med Res Opin, 2010	IA05	NCT00079937	April 2004 – March 2008	Omalizumab vs. Placebo for children with severe allergic asthma
Subcutaneous mepolizumab in children aged 6 to 11 years with severe eosinophilic asthma, A. Gupta, I.P. Pharm, D. Austin, R.G. Price, R. Kempsford, J. Steinfeld, E.S. Bradford,S.W. Yancey, Pediatric Pulmonology, 2019	NA	NCT02377427	August 25, 2015 – January 31, 2018	Mepolizumab in children with severe Eosinophilic asthma
Long-term safety and pharmacodynamics of mepolizumab in children with severe asthma with an eosinophilic phenotype, A. Gupta, M. Ikeda, B. Geng, J. Azmi, R.G. Price, E.S. Bradford, S.W. Yancey, J. Steinfeld, J Allergy Clin Immunol, 2019	NA	NCT02377427	August 25, 2015 – January 31, 2018	Mepolizumab in children with severe Eosinophilic asthma

Quality assessment

Literature search adhered to the highest standards for conducting and reporting. The SLR was re-fitted for the purpose of the assessment in Denmark using the same methodology.

Unpublished data

All subgroup analyses of Liberty Asthma VOYAGE are unpublished analyses.

Following dataset are planned for publication:

- VOYAGE Allergic Asthma subgroup
- VOYAGE Efficacy in asthma in patients with atopic comorbidities
- VOYAGE FeNO subgroup
- VOYAGE Lung Function Parameters

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Appendix B Main characteristics of included studies

Table 88 Study characteristics for Liberty Asthma VOYAGE

Trial name: Liberty Asthma VOYAGE	NCT number: 02948959
Objective	*To evaluate the efficacy of dupilumab in children 6 to <12 years of age with uncontrolled persistent asthma*
Publications – title, author, journal, year	*Dupilumab in Children with Uncontrolled Moderate-to-Severe Asthma, L.B. Bacharier, J.F. Maspero, C.H. Katelaris, A.G. Fiocchi, R. Gagnon, I. de Mir, N. Jain, L.D. Sher, X. Mao, D. Liu, Y. Zhang, A.H. Khan, U. Kapoor, F.A. Khokhar, P.J. Rowe, Y. Deniz, M. Ruddy, E. Laws, N. Patel, D.M. Weinreich, G.D. Yancopoulos, N. Amin, L.P. Mannent, D.J. Lederer, and M. Hardin, N. Eng. Jour. Medicine, 2021*
Study type and design	*A phase 3 multinational, multicentre, randomized, double-blind, placebo-controlled clinical trial designed to demonstrate the efficacy and safety of dupilumab administered for up to 52 weeks in addition to standard of care maintenance therapy in children 6 to <12 years of age with uncontrolled moderate-to-severe asthma*
Sample size (n)	*408*

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Trial name: Liberty Asthma VOYAGE	NCT number: 02948959

Main inclusion and exclusion criteria

Inclusion criteria :

Children 6 to <12 years of age, with a physician diagnosis of persistent asthma for ≥12 months prior to Screening, based on clinical history and examination, pulmonary function parameters according to Global initiative for asthma (GINA) 2015 Guidelines and the following criteria:

- *Existing background therapy of medium-dose inhaled corticosteroids (ICS) with second controller medication (ie, long-acting β2 agonist [LABA], leukotriene receptor antagonist [LTRA], long acting muscarinic antagonist [LAMA], or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller, for at least 3 months with a stable dose ≥1 month prior to Screening Visit 1.*
- *Pre-bronchodilator forced expiratory volume in 1 second (FEV1) ≤95% of predicted normal or pre bronchodilator FEV1/forced vital capacity (FVC) ratio <0.85 at Screening and Baseline Visits.*
- *Reversibility of at least 10% in FEV1 after the administration of 200 to 400 mcg (2 to 4 puff inhalations with metered-dose inhaler [MDI]) of albuterol/salbutamol or 45 to 90 mcg (2 to 4 puffs with MDI) of levalbuterol/levosalbutamol reliever medication before randomization (up to 3 opportunities during the same visit are allowed with a maximum of 12 puffs of reliever medication if tolerated by the patient).*
- *Must have experienced, within 1 year prior to Screening Visit 1, any of the following events:*
  - *Treatment with a systemic corticosteroid (SCS, oral or parenteral), as prescribed by a healthcare professional for worsening asthma at least once or,*
  - *Hospitalization or emergency room visit for worsening asthma.*
- *Evidence of uncontrolled asthma, with at least one of the following criteria during the 4 (±1) weeks Screening Period:*
  - *Asthma Control Questionnaire-Interviewer Administered (ACQ-IA) ACQ-5 score ≥1.5 on at least one day of the Screening Period.*
  - *Use of reliever medication (ie, albuterol/salbutamol or levalbuterol/levosalbutamol), other than as a preventive for exercise induced bronchospasm, on 3 or more days per week, in at least one week during the Screening Period.*
  - *Sleep awakening due to asthma symptoms requiring use of reliever medication at least once during the Screening Period.*
  - *Asthma symptoms 3 or more days per week in at least one week during the Screening Period*

Exclusion criteria:

- *Patients <6 or ≥12 years of age.*
- *Patients with <16 kg bodyweight.*
- *Any other chronic lung disease (cystic fibrosis, bronchopulmonary dysplasia, etc.), which may impair lung function.*
- *A subject with any history of life threatening asthma (ie, extreme exacerbation that requires intubation).*
- *Co-morbid disease that might interfere with the evaluation of investigational medicinal product (IMP)*

Trial name: Liberty Asthma VOYAGE	NCT number: 02948959
Intervention	The intervention was dupilumab and dosage was stratified by weight. Patients >30kg received 200 mg doses, while patients ≤30kg received 100 mg doses. Patients and investigators were blinded to the treatment, but not to the dose, meaning they were aware of whether they received/administered 200/100 mg. Out of 408 patients, 273 were allocated to the dupilumab arm.
Comparator(s)	*The comparator in the study was placebo and* dosage was stratified by weight. Patients >30kg received 200 mg doses, while patients ≤30kg received 100 mg doses. *Out of 408 patients, 135 was allocated to the placebo arm.*
Follow-up time	*Median follow-up duration was 365 days*
Is the study used in the health economic model?	*Yes*

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Trial name: Liberty Asthma VOYAGE	NCT number: 02948959

Primary, secondary and exploratory endpoints

Primary Outcome Measures :

1. *Annualized rate of severe exacerbation events during the placebo-controlled treatment period [Time Frame: Baseline, Week 52]*

Secondary Outcome Measures :

1. *Change from baseline in pre-bronchodilator % predicted forced expiratory volume in 1 second (FEV1) [Time Frame: Baseline, Week 12]*
2. *Change from baseline in pre-bronchodilator % predicted FEV1 [Time Frame: Baseline, Weeks 2, 4, 8, 24, 36, 52]*
3. *Time to first severe exacerbation event [Time Frame: Up to 52 weeks]*
4. *Time to first loss of asthma control event [Time Frame: Up to 52 weeks]*
5. *Change from baseline in other lung function measurements: absolute and relative FEV1 [Time Frame: Baseline, Weeks 2, 4, 8, 12, 24, 36, 52]*
6. *Change from baseline in other lung function measurements: AM/PM peak expiratory flow (PEF) [Time Frame: Baseline, Weeks 2, 4, 8, 12, 24, 36, 52]*
7. *Change from baseline in other lung function measurements: Forced Vital Capacity [Time Frame: Baseline, Weeks 2, 4, 8, 12, 24, 36, 52]*
8. *Change from baseline in other lung function measurements: Forced expiratory flow (FEF) 25-75% [Time Frame: Baseline, Weeks 2, 4, 8, 12, 24, 36, 52]*
9. *Change from baseline in other lung function measurements: Post bronchodilator % predicted FEV1 [Time Frame: Baseline, Weeks 2, 4, 8, 12, 24, 36, 52]*
10. *The effect of dupilumab on healthcare resource utilization [Time Frame: Baseline, Week 52]*
11. *Change from baseline in morning asthma symptom score [Time Frame: Baseline, Weeks 2, 4, 8, 12, 24, 36, 52]*
12. *Change from baseline in evening asthma symptom score [Time Frame: Baseline, Weeks 2, 4, 8, 12, 24, 36, 52]*
13. *Number of nocturnal awakenings due to asthma symptoms requiring the use of reliever medication [Time Frame: Baseline, Weeks 2, 4, 8, 12, 24, 36, 52]*
14. *Number of rescue medication inhalations [Time Frame: Baseline, Week 2, 4, 8, 12, 24, 36, 52]*
15. *Assessment of Patient Reported Outcomes: Asthma control questionnaire [Time Frame: Baseline, Weeks 2, 4, 8,12, 24, 36, 52,]*
16. *Assessment of Patient Reported Outcomes: Pediatric Asthma quality of life questionnaire [Time Frame: Baseline, Weeks 12, 24, 36, 52, 64]*
17. *Assessment of IgG responses to vaccination during dupilumab treatment (may be analyzed as exploratory endpoint if insufficient power) [Time Frame: 2 blood draws per vaccine scheduled:1 prevaccination and 1 post-vaccination.]*
18. *Change from baseline in fractional exhaled nitric oxide (FeNO) prior to spirometry [Time Frame: Baseline, Week 12]*
19. *Adverse Events [Time Frame: Up to Week 64]*
20. *Anti-Drug Antibodies [Time Frame: Baseline, Weeks 12, 24, 52, 64]*
21. *Serum Dupilumab Concentrations [Time Frame: Baseline, Weeks 6, 12, 24, 52, 64]*

Trial name: Liberty Asthma VOYAGE	NCT number: 02948959
Method of analysis	*There were 2 primary efficacy populations:* *• Type 2 inflammatory asthma phenotype population defined as the randomized patients with baseline blood eosinophil count ≥0.15 Giga/L or baseline FeNO ≥20 ppb;* *• Baseline blood eosinophil count ≥0.3 Giga/L population defined as the randomized patients with baseline blood eosinophil count ≥0.3 Giga/L.* *The primary efficacy endpoint, annualized rate of severe exacerbation events, was analyzed using a negative binominal regression model. The analysis for the annualized severe exacerbation rate was performed in the primary efficacy populations (the population with the type 2 inflammatory asthma phenotype and the population with baseline blood eosinophil count ≥0.3 Giga/L) and in additional efficacy populations identified on the basis of type 2 inflammatory biomarkers including either baseline blood eosinophil count ≥0.15 Giga/L or baseline FeNO ≥20 ppb independently, as well as the ITT population.* *For secondary efficacy endpoints MMRM approach was taken.* *The safety analysis was conducted for the safety population, which consisted of all patients who actually received at least 1 dose or part of a dose.*
Subgroup analyses	• *The population with baseline blood eosinophil count ≥0.15 Giga/L defined as the randomized patients with baseline blood eosinophil count ≥0.15 Giga/L.* • *The population with baseline FeNO ≥20 ppb defined as the randomized patients with baseline FeNO ≥20 ppb.* • *The full intent-to-treat (ITT) population, defined as all randomized patients.*
Other relevant information	*No*

Table 89. Main study characteristics for omalizumab

Trial name: OMALIZUMAB	NCT number: NCT00079937
Objective	*To evaluate the efficacy of omalizumab in children 6 to <12 years of age with inadequately controlled allergic (IgE-mediated) asthma*
Publications – title, author, journal, year	• *B. Lanier, T. Bridges, M. Kulus, A. F. Taylor, I. Berhane and C. F. Vidaurre, Omalizumb for the treatment of exacerbations in children with inadequately controlled allergi (IgE-mediated) asthma, 2010, J Allergy Clin Immunol, doi: 10.1016/j.jaci.2009.09.021.* • *M. Kulus, J. Hebert, E. Garcia, A. Fowler Taylor, C. Fernandez Vidaurre, M. Blogg, Omalizumab in children with inadequately controlled severe allergic (IgE-mediated) asthma, 2009, Curr Med Res Opin, doi: 10.1185/03007991003771338*
Study type and design	*Randomized, double-blind, placebo-controlled, parallel group, phase 3 trial*
Sample size (n)	*628*

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Trial name: OMALIZUMAB	NCT number: NCT00079937

Main inclusion and exclusion criteria

Inclusion criteria:

- Parent or legal guardian was informed of the study procedures and medications and gave written informed consent.
- Outpatient males and females aged 6 to < 12 years on study entry, with body weight between 20 and 150 kg.
- Total serum IgE level ≥ 30 to ≤ 1300 IU.
- Diagnosis of allergic asthma ≥ 1 year duration, according to American Thoracic Society (ATS) criteria, and a screening history consistent with clinical features of moderate or severe persistent asthma according to National Heart Lung and Blood Institute (NHLBI) guidelines.
- Positive prick skin test to at least one perennial allergen, documented within the past 2 years or taken at Screening. A radioallergosorbent test (RAST) could have been performed for patients with a borderline skin prick test result after consultation with Novartis clinical personnel.
- Patients with ≥ 12% increase in forced expiratory volume in 1 second (FEV1) over starting value within 30 minutes of taking up to 4 puffs (4x100 µg) salbutamol (albuterol) or nebulized salbutamol up to 5 mg (or equivalent of alternative B2-agonist) documented within the past year, at screening, during the run-in period, or prior to randomization. Patients were not to take their long acting B2-agonist (LABA) medication within 12 hours of reversibility testing.
- Clinical features of moderate or severe persistent asthma (at least step 3) despite therapy at step 3 or 4 (at least medium dose inhaled corticosteroid (ICS) - fluticasone dry-powder inhaler (DPI) ≥ 200 mg/day or equivalent with or without other controller medications).
- Documented history of experiencing asthma exacerbations and demonstrated inadequate symptom control during the last 4 weeks of run-in despite receiving an equivalent dose of fluticasone DPI ≥ 200 mg/day total daily ex-valve dose.

Exclusion criteria:

- Patients who received systemic corticosteroids for reasons other than asthma, beta-adrenergic antagonists by any route, anticholinergics within 24 hours of Screening, methotrexate, gold salts, cyclosporin or troleandomycin, or had received desensitization therapy with less than 3 months of stable maintenance doses prior to Screening.
- Patients with a history of food or drug related severe anaphylactoid or anaphylactic reaction, a history of allergy to antibiotics, with aspirin or other non-steroidal anti-inflammatory drugs (NSAID)-related asthma (unless the NSAID could be avoided), with active lung disease or acute sinusitis/chest infection, elevated serum IgE levels for other reasons, presence/history of a clinically significant uncontrolled systemic disease, cancer, abnormal, electrocardiogram (ECG) in the previous month, or platelets ≤ 100 x 109/L or clinically significant laboratory abnormalities at Screening.

Intervention	*Omalizumab*
Comparator(s)	*Placebo*
Follow-up time	*52 weeks*

Trial name: OMALIZUMAB	NCT number: NCT00079937
Is the study used in the health economic model?	*Yes*

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Primary, secondary and exploratory endpoints

Primary

1. *Rate of Clinically Significant Asthma Exacerbations Per Patient in the 24-week Fixed-dose Steroid Treatment Period [Time Frame: Baseline to end of the fixed-dose steroid treatment period (Week 24)]*

   A clinically significant asthma exacerbation was defined as a worsening of asthma symptoms, as judged clinically by the investigator, requiring doubling of the baseline inhaled corticosteroid dose and/or treatment with systemic rescue corticosteroids for at least 3 days. The exacerbations rate per patient was derived using Poisson model adjusted by time at risk and the following covariates: country, exacerbation history, and dose schedule. A patient's person-days at risk was taken as the total amount of time (in days) he/she spent in the 24-week fixed-dose steroid treatment period.

2. *Percentage of Participants With at Least 1 Adverse Event [Time Frame: Baseline to end of the study (Week 68)]*

Secondary

3. *Change in Mean Nocturnal Asthma Symptom Score From Baseline to the End (Last 4 Weeks) of the 24-week Fixed-dose Steroid Treatment Period [Time Frame: Baseline to the end (last 4 weeks) of the 24-week fixed-dose steroid treatment period]*

   Nocturnal asthma symptom was measured daily on a scale of 0 to 4 in response to the question "How did you sleep last night?", with 0 as the best response and 4 as the worst response. The mean of the last 4 weeks of the 24-week fixed-dose steroid treatment period was calculated; for patients who discontinued prematurely, the mean of the last 28 days before discontinuation was calculated. A negative change in mean score indicated improvement.

4. *Rate of Clinically Significant Asthma Exacerbations Per Patient in the 52-week Treatment Period [Time Frame: Baseline to end of the treatment period (Week 52)]*

   A clinically significant asthma exacerbation was defined as a worsening of asthma symptoms, as judged clinically by the investigator, requiring doubling of the baseline inhaled corticosteroid dose and/or treatment with systemic rescue corticosteroids for at least 3 days. The exacerbations rate per patient was derived using Poisson model adjusted by time at risk and the following covariates: country, exacerbation history, and dose schedule. A patient's person-days at risk was taken as the total amount of time (in days) he/she spent in the 52-week treatment period.

5. *Change in Mean Daily Number of Puffs of Asthma Rescue Medication From Baseline to the End (Last 4 Weeks) of the 24-week Fixed-dose Steroid Treatment Period [Time Frame: Baseline to the end (last 4 weeks) of the 24-week fixed-dose steroid treatment period]*

   Patients were instructed to record the number of puffs of rescue medication they took twice daily in a diary. The mean daily number of puffs during the last 4 weeks of the 24-week fixed-dose steroid treatment period was calculated; for patients who discontinued prematurely, the mean of the last 28 days before discontinuation was calculated. A negative change in mean daily number of puffs indicated reduced use of rescue medication.

6. *Change in Pediatric Asthma Quality of Life Questionnaire (Standardized) [PAQLQ(S)] Scores From Baseline to the End of the 24-week Fixed-dose Steroid Treatment Period (Week 24) [Time Frame: Baseline to the end of the 24-week fixed-dose steroid*

Trial name: OMALIZUMAB	NCT number: NCT00079937
	treatment period (Week 24)] *PAQLQ measures functional problems that are most troublesome to children with asthma. PAQLQ has 23 questions in 3 domains (activity limitation=5, emotional function=8, symptoms=10). Patients responded to each question on a 7-point Likert scale. Overall PAQLQ score is mean of 23 questions; each domain score is mean of questions in that domain. Minimum possible value is 1 (maximum impairment); maximum possible value is 7 (no impairment). Positive change indicated improvement. The analysis included country, baseline PAQLQ value, and dosing schedule (2-weekly/4-weekly) as factors and covariates.*
Method of analysis	*Statistical differences between group baseline characteristics were tested using the F-test, chi-squared test and Fisher's exact test, as appropriate.* *Rate of clinically significant asthma exacerbations over 24 and 52 weeks were compared between treatment groups using a two-sided test at a=0.05 with a generalized Poisson regression model. The rate ratio (RR) of exacerbations between the treatment groups and 95% confidence interval (CI) were obtained.* *For patients who discontinued early, exacerbation data were imputed for clinically significant exacerbations over 24 and 52 weeks (one added to the total number for patients who discontinued prematurely, unless they had an exacerbation ≤7 days prior to discontinuation).* *The percentage change from baseline in ICS dose was compared using the van Elteren test: a non-parametric test that compares treatments in the presence of blocking (an extension of Wilcoxon's rank-sum test); percent change in ICS dose for patients who discontinued before the 28-week adjustable-steroid phase was imputed as zero. The numbers of patients rated as excellent or good according to the physician's GETE were compared using the Cochran Mantel Haenszel test.* *Assessment of safety was based on the frequency of all AEs. Statistical differences between the frequency of AEs reported in the omalizumab and placebo groups were calculated using Fisher's exact test.*
Subgroup analyses	*Children with inadequately controlled severe asthma, despite receiving high-dose ICS (≥500 mg · day^{-1} FP or equivalent) and a LABA, with or without other controller medications, Kulus et al. 2010 (16)*
Other relevant information	*No*

Table 90 Main study characteristics for mepolizumab

Trial name: MEPOLIZUMAB	NCT number: 02377427
Objective	*To evaluate the pharmacokinetics and pharmacodynamics, along with long-term safety of mepolizumab in children 6 to <12 years of age with severe eosinophilic asthma*
Publications – title, author, journal, year	• *Gupta A, Pouliquen I, Austin D, Price RG, Kempsford R, Steinfeld J, Bradford ES, Yancey SW. Subcutaneous mepolizumab in children aged 6 to 11 years with severe eosinophilic asthma. Pediatr Pulmonol. 2019 Dec;54(12):1957-1967. doi: 10.1002/ppul.24508. Epub 2019 Sep 9. PMID: 31502421; PMCID: PMC6972599.* • *Gupta A, Ikeda M, Geng B, Azmi J, Price RG, Bradford ES, Yancey SW, Steinfeld J. Long-term safety and pharmacodynamics of mepolizumab in children with severe asthma with an eosinophilic phenotype. J Allergy Clin Immunol. 2019 Nov;144(5):1336-1342.e7. doi: 10.1016/j.jaci.2019.08.005. Epub 2019 Aug 16. PMID: 31425781.*
Study type and design	*An open-label, non-randomized, multinational interventional study*
Sample size (n)	*36*

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Main inclusion and exclusion criteria	**Inclusion Criteria:** • Between 6 and 11 years of age inclusive, at the time of screening. • Diagnosis of severe asthma, defined by the regional asthma guidelines (i.e., National Institute of Health (NIH), Global Initiative for Asthma (GINA), etc.), for at least 12 months prior to Visit 1. If the participant is naïve to the study site, the participant/guardian must self-report a physician diagnosis of asthma and the investigator must confirm by review of medical history with the participant/guardian. • Eosinophilic airway inflammation that is related to asthma characterized as eosinophilic in nature as indicated by: elevated peripheral blood eosinophil count of >=300 cells per microliter (cells/µL) demonstrated in the past 12 months OR elevated peripheral blood eosinophil count of >=150/µL at visit 1. • A well-documented requirement for regular treatment with inhaled corticosteroid (>200 µg/day fluticasone propionate drug powder inhaler [DPI] or equivalent daily) in the 12 months prior to Visit 1 with or without maintenance oral corticosteroids (OCS). The ICS dose should represent medium or high dose in children aged 6-11 years of age [GINA, 2015]. • Current treatment with an additional controller medication for at least 3 months or a documented failure in the past 12 months of an additional controller medication for at least 3 successive months. [e.g., long-acting beta-2-agonist (LABA), leukotriene receptor antagonist (LTRA), or theophylline.] • Forced expiratory volume in one second (FEV1): Persistent airflow obstruction at either Visit 1 or Visit 2 (FEV1 performed prior to first dose of study medication) as indicated by: A pre-bronchodilator FEV1 <110% predicted (Quanjer, 2012) OR FEV1: Forced vital capacity (FVC) ratio <0.8. • Previously confirmed history of two or more exacerbations requiring treatment with systemic corticosteroids (CS) (intramuscular [IM], intravenous, or oral), in the 12 months prior to visit 1, despite the use of high-dose inhaled corticosteroids (ICS). For participants receiving maintenance CS, the CS treatment for the exacerbations must have been a two-fold increase or greater in the dose. • No changes in the dose or regimen of baseline ICS and/or additional controller medication during the run-in period. • Male or female: Females of childbearing potential must commit to consistent and correct use of an acceptable method of contraception for the duration of the trial and for 4 months after the last dose of investigational product. A urine pregnancy test is required of girls of childbearing potential. This test will be performed at the initial screening visit (visit 1) and will be performed at each scheduled study visit prior to the administration of investigational product, and during the early withdrawal and follow-up visits. • Parent(s)/guardian able to give written informed consent prior to participation in the study, which will include the ability to comply with the requirements and restrictions listed in the consent form. If applicable, the participant must be able and willing to give assent to take part in the study according to the local requirement. • For Part B: The subject has completed all study assessments up-to and including Visit 8 and received all 3 doses of investigational product (IP) in Part A • For Part B: The Principal Investigator (PI) has performed a benefit/risk assessment and this assessment supports continued therapy with mepolizumab. • The subject's parents (or guardian) have given consent and the subject has given assent for continued treatment **Exclusion Criteria:** • Participants with any history of life threatening asthma (e.g. requiring intubation), immunosuppressive medications intake or immunodeficiency disorder.

Trial name: MEPOLIZUMAB	NCT number: 02377427

- Participants with any medical condition or circumstance making the volunteer unsuitable for participation in the study.
- Significant abnormality of rate, interval, conduction or rhythm in the 12-lead electrocardiogram (ECG), determined by the investigator in conjunction with the age and gender of the child at Visit 1.
- Alanine aminotransferase (ALT), and bilirubin >2x upper limit of normal (ULN) (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at Visit 1.
- Positive Hepatitis B Surface Antigen or positive Hepatitis C antibody at Visit 1.
- Parent/guardian has a history of psychiatric disease, intellectual deficiency, substance abuse, or other condition (e.g. inability to read, comprehend and write) which will limit the validity of consent to participate in this study.
- Unwillingness or inability of the participant or parent/guardian to follow the procedures outlined in the protocol.
- Participant who is mentally or legally incapacitated.
- Children who are wards of the state or government.
- A participant will not be eligible for this study if he/she is an immediate family member of the participating investigator, sub-investigator, study coordinator, or employee of the participating investigator.
- Omalizumab: Participants who have received omalizumab within 130 days of Visit 1.
- Other Biologics: Participants who have received any biological (other than omalizumab) to treat inflammatory disease within 5 half-lives of visit 1.
- History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.
- Hypersensitivity: Participants with allergy/intolerance to a monoclonal antibody or biologic.
- The participant has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).

Intervention	The intervention was 40 mg of mepolizumab for children with a body weight <40kg or 100 mg for children with a body weight ≥40kg, via subcutaneous injections administered every 4 weeks for 12 weeks. Some patients received both dosages, as they went from <40kg to ≥40kg during the study.
Comparator(s)	*Single-arm study*
Follow-up time	*72 weeks*
Is the study used in the health economic model?	*Yes*

Primary, secondary and exploratory endpoints

Primary Outcome Measures :

1. Maximum Plasma Concentration (Cmax) of Mepolizumab for Part A [Time Frame: Pre-dose on Weeks 4 and 8; Weeks 9, 12, 16 and 20 post-dose]
2. Area Under Concentration Time Curve to Infinity (AUC [0-inf]) of Mepolizumab for Part A [Time Frame: Pre-dose on Weeks 4 and 8; Weeks 9, 12, 16 and 20 post-dose]
3. Terminal Phase Elimination Half-life (T1/2) of Mepolizumab During Treatment Period for Part A [Time Frame: Pre-dose on Weeks 4 and 8; Weeks 9, 12, 16 and 20 post-dose]
4. Plasma Apparent Clearance (CL/F) of Mepolizumab in Part A [Time Frame: Pre-dose on Weeks 4 and 8; Weeks 9, 12, 16 and 20 post-dose]
5. Ratio to Baseline in Absolute Blood Eosinophil Count at Week 12 for Part A [Time Frame: Baseline and Week 12]
6. Number of Participants With on Treatment Serious Adverse Events (SAEs) and Non-SAEs for Part B [Time Frame: From Week 20 and up to Week 72]
7. Number of Participants With Positive Anti-mepolizumab Binding Antibodies and Neutralizing Antibodies Response for Part B [Time Frame: From Week 20 and up to Week 80]
8. Change From Baseline in Sitting Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) for Part B [Time Frame: Baseline and Weeks 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 80]
9. Change From Baseline in Sitting Pulse Rate for Part B [Time Frame: Baseline and Weeks 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 80]
10. Number of Participants With Any Time Change From Baseline Relative to Normal Range in Clinical Chemistry Parameters for Part B [Time Frame: Baseline, from Week 20 and up to Week 72]
11. Number of Participants With Any Time Change From Baseline Relative to Normal Range in Hematology Parameters for Part B [Time Frame: Baseline, from Week 20 and up to Week 80]
12. Number of Participants With Abnormal Findings for Urinalysis Parameters in Part B [Time Frame: From Week 20 and up to Week 72]

Secondary Outcome Measures :

1. Body Weight-adjusted Apparent Clearance of Mepolizumab for Part A [Time Frame: Pre-dose on Weeks 4 and 8; Weeks 9, 12, 16 and 20 post-dose]
2. Change From Baseline in Asthma Control Questionnaire-7 (ACQ-7) at Week 12 in Part A [Time Frame: Baseline and Week 12]
3. Change From Baseline in Asthma Control Questionnaire-7 (ACQ-7) at Weeks 4,8,16 and 20 in Part A [Time Frame: Baseline and Weeks 4,8,16 and 20]
4. Change From Baseline in Childhood Asthma Control Test (C-ACT) at Week 12 for Part A [Time Frame: Baseline and Week 12]
5. Change From Baseline in C-ACT at Weeks 4,8,16 and 20 in Part A [Time Frame: Baseline and Weeks 4,8,16 and 20]
6. Number of Participants With on Treatment SAEs and Non-SAEs in Part A [Time Frame: Up to Week 20]

Trial name: MEPOLIZUMAB	NCT number: 02377427

7. Number of Participants With Any Time Change From Baseline Relative to Normal Range in Hematology Parameters in Part A [Time Frame: Baseline and up to Week 20]
8. Number of Participants With Any Time Change From Baseline Relative to Normal Range in Clinical Chemistry Parameters in Part A [Time Frame: Baseline and up to Week 20]
9. Number of Participants With Abnormal Findings for Urinalysis in Part A [Time Frame: Up to Week 20]
10. Number of Participants With Positive Anti-mepolizumab Binding Antibodies and Neutralizing Antibodies Response in Part A [Time Frame: Baseline and Weeks 16 and 20]
11. Change From Baseline in Sitting SBP and DBP in Part A [Time Frame: Baseline and Weeks 4, 8, 9, 12, 16 and 20]
12. Change From Baseline in Sitting Pulse Rate in Part A [Time Frame: Baseline and Weeks 4, 8, 9, 12, 16 and 20]
13. Ratio to Baseline in Absolute Blood Eosinophil Count at Weeks 32, 44, 56, 68, 72 and 80 for Part B [Time Frame: Baseline and Weeks 32, 44, 56, 68, 72 and 80]

Method of analysis	Part A; Mepolizumab plasma PK concentrations were analyzed by nonlinear mixed-effect modeling methods (SAS Institute Inc, Cary, NC). A two-compartment model with first-order absorption and elimination was used with PK distribution parameters and bioavailability fixed to previously estimated adult values. Bodyweight was incorporated into the model using physiological allometry with allometric exponents for clearance and volumes estimated. Final model appropriateness was assessed using goodness of fit plots, simulations, and statistical tests. The ratio of blood eosinophil count at week 12 to baseline was summarized descriptively, and the ratio at each visit to baseline presented graphically. Bodyweight-adjusted apparent clearance point estimates with 90% CIs in children 6 to 11 years were presented alongside the historical estimated adult value of 0.29 L/day (unpublished data) with a proposed 80% to 125% interval around this estimate of 0.23 to 0.36 L/day. An exploratory population PK analysis using the most recent mepolizumab population PK model with minimal estimation (absolute bioavailability, allometric exponents, and residual error) was conducted using NONMEM software (version 7.2; ICON Development Solutions, Ellicott City, MD). Part B: All statistical analyses were performed by using the safety population (all children who received >1 dose of mepolizumab within part B). Endpoints were summarized by using appropriate descriptive statistics (mean/geometric mean, median, SD, and range). AEs were summarized by using the Medical Dictionary for Regulatory Activities Primary System Organ Class and Preferred Terms. Annualized exacerbation rates were determined by using a negative binomial generalize linear model with logarithm of time as an offset variable, from which estimates rates per year and 95% CIs were calculated. For blood eosinophil counts, the ratio to baseline was summarized by visit; if a result of zero was recorded, a small value (half the minimum nonzero result) was imputed before log-transformation. For blood eosinophil counts and asthma control questionnaire scores, baseline was defined as the value recorded before the first mepolizumab treatment in part A (overall study week 0). All statistical analyses were performed with SAS software (version 9.4; SAS Institute, Cary, NC).
Subgroup analyses	children with severe asthma with an eosinophilic phenotype
Other relevant information	No

Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Liberty Asthma VOYAGE vs. IA05 (Kulus et al., 2010(16)) (severe allergic IgE asthma subgroup)

Table 91. Baseline characteristics of patients included in Liberty Asthma VOYAGE and IA05 for the comparative analysis of efficacy and safety

Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety				
	Liberty Asthma VOYAGE (Severe allergic subgroup)		IA05 (Kulus et al., 2010) (mITT)(16)	
	Placebo (n=63)	Dupilumab (n=115)	Placebo (n = 76)	Omalizumab (n =159)
Mean age (mean (SD))	[redacted]	[redacted]	8.6 (1.7)	9.1 (1.7)
Gender (% female)	[redacted]	[redacted]	31.6%	35.8%
Race (% white)	[redacted]	[redacted]	63.2%	57.9%
Mean weight (kg (SD))	[redacted]	[redacted]	NA	NA
High ICS dose level at baseline (%)	[redacted]	[redacted]	NA	NA
Mean time since first diagnosis of asthma (years (SD))	[redacted]	[redacted]	NA	NA
Number of severe asthma exacerbation experienced in the past year	[redacted]	[redacted]	NA	NA
Mean FEV1% predicted	[redacted]	[redacted]	82.6 (19.5)	81.8 (17.5)
Mean FEV_1 reversibility (% (SD))	[redacted]	[redacted]	25.1% (14.8)	29.4 (19.9)
Blood Eosinophil (cells/µL (SD))	[redacted]	[redacted]	NA	NA
Mean FeNO (ppb (SD))	[redacted]	[redacted]	NA	NA
Mean total IgE (IU/mL (SD))	[redacted]	[redacted]	414.0 (305.6)	452.4 (328.3)
Baseline Global PAQLQ-IA score	[redacted]	[redacted]	NA	NA

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Baseline Global PRQLQ-IA score	[redacted]	[redacted]	NA	NA
Ongoing atopic medical conditions [n (%)]	62 (98.4%)	115 (100%)	NA	NA
Ongoing atopic dermatitis , *[n (%)]*	19 (30.2%)	45 (39.1%)	NA	NA
Ongoing allergic conjunctivitis *[n (%)]*	13 (20.6%)	26 (22.6%)	NA	NA
Ongoing allergic rhinitis , *[n (%)]*	51 (81.0%)	96 (83.5%)	NA	NA
Ongoing eosinophilic esophagitis , *[n (%)]*	0	1 (0.9%)	NA	NA
Ongoing food allergy , *[n (%)]*	8 (12.7%)	22 (19.1%)	NA	NA
Ongoing hives *[n (%)]*	3 (4.8%)	13 (11.3%)	NA	NA

Liberty Asthma VOYAGE vs. Mepolizumab (Severe eosinophilic asthma)

Table 92. Baseline characteristics of patients included in Liberty Asthma VOYAGE and mepolizumab-trial (18) for the comparative analysis of efficacy and safety

Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety				
	Liberty Asthma VOYAGE (Severe eosinophilic subgroup)		**Mepolizumab (18)**	
	Placebo (n=130)	Dupilumab (n=254)	Mepolizumab 40mg (n=26)	Mepolizumab 100mg (n=10)
Mean age (mean (SD))	[redacted]	[redacted]	8.0 (1.8)	10.0 (1.3)
Gender (% female)	[redacted]	[redacted]	23%	50%
Race (% white)	[redacted]	[redacted]	NA	NA
Mean weight (kg (SD))	[redacted]	[redacted]	27.4 (4.7)	49.5 (6.3)
High ICS dose level at baseline (%)	[redacted]	[redacted]	NA	NA
Mean time since first diagnosis of asthma (years (SD))	[redacted]	[redacted]	NA	NA

Number of severe asthma exacerbation experienced in the past year	[redacted]	[redacted]	NA	NA
Mean FEV1% predicted	[redacted]	[redacted]	89 (16.9)	92 (6.9)
Mean FEV_1 reversibility (% (SD))	[redacted]	[redacted]	NA	NA
Blood Eosinophil (cells/µL (SD))	[redacted]	[redacted]	386 (0.75*)	331 (0.91*)
Mean FeNO (ppb (SD))	[redacted]	[redacted]	NA	NA
Mean total IgE (IU/mL (SD))	[redacted]	[redacted]	336 (1.48*)	379 (1.09*)
Baseline Global PAQLQ-IA score	[redacted]	[redacted]	NA	NA
Baseline Global PRQLQ-IA score	[redacted]	[redacted]	NA	NA
Ongoing atopic dermatitis [n (%)]	[redacted]	[redacted]	NA	NA
Ongoing allergic conjunctivitis [n (%)]	[redacted]	[redacted]	NA	NA
Ongoing allergic rhinitis, [n (%)]	[redacted]	[redacted]	NA	NA

Note: *, SD logs

Liberty Asthma VOYAGE (Severe asthma with elevated FeNO)

Table 93. Baseline characteristics of patients in Liberty Asthma VOYAGE, severe asthma with elevated FeNO expression subgroup

Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety		
	Liberty Asthma VOYAGE (Severe asthma with elevated FeNO subgroup)	
	Placebo (n=130)	**Dupilumab (n=254)**
Mean age (mean (SD))	[redacted]	[redacted]
Gender (% female)	[redacted]	[redacted]
Race (% white)	[redacted]	[redacted]

Mean weight (kg (SD))	[redacted]	[redacted]
High ICS dose level at baseline (%)	[redacted]	[redacted]
Mean time since first diagnosis of asthma (years (SD))	[redacted]	[redacted]
Number of severe asthma exacerbation experienced in the past year	[redacted]	[redacted]
Mean FEV1% predicted	[redacted]	[redacted]
Mean FEV_1 reversibility (% (SD))	[redacted]	[redacted]
Blood Eosinophil (cells/µL (SD))	[redacted]	[redacted]
Mean FeNO (ppb (SD))	[redacted]	[redacted]
Mean total IgE (IU/mL (SD))	[redacted]	[redacted]
Baseline Global PAQLQ-IA score	[redacted]	[redacted]
Baseline Global PRQLQ-IA score	[redacted]	[redacted]
Ongoing atopic dermatitis [n (%)]	[redacted]	[redacted]
Ongoing allergic conjunctivitis [n (%)]	[redacted]	[redacted]
Ongoing allergic rhinitis, [n (%)]	[redacted]	[redacted]

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Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
Severe asthma exacerbation	The frequency of severe asthma exacerbations.	Rate of asthma exacerbation has been used in prior DMC submission for asthma and for treatment guideline protocol (22, 23)	Used in prior DMC submission for asthma and for treatment guideline protocol (22, 23)
Lung function	% patients with >=200mL improvement in FEV1 at week 12 (95% CI)		The minimal clinically important difference for % patients with >=200mL improvement in FEV1 is 15% (19, 50)
FEV_1	FEV1 is the volume of air that can be forcibly expired in one second after a full inspiration.	Used in prior DMC submission for asthma and for treatment guideline protocol (22, 23)	The minimal clinically important difference for FEV_1 is 12% for children (19, 50)
ACQ-7-IA	ACQ is a patient-reported tool to assess asthma control in patient ≥ 6 years of age. It comprises the following seven questions, of which the mean of the results is the overall score (0 = well-controlled asthma and 6 = extremely poorly controlled asthma)	The Asthma Control Questionnaire (ACQ) has been shown to be a valid, reliable instrument that allows accurate and reproducible assessment of asthma control that compares favorably with other commonly used instruments (101). ACQ is used prior in DMC submissions for asthma and for treatment guideline protocol (50)	The minimal clinically important difference for ACQ is 0.5 (19, 50)
Pediatric Asthma Quality of Life Questionnaire (PAQLQ(S))	Pediatric Asthma Quality of Life Questionnaire	PAQLQ is a validated tool, which was developed to measure the problems that children with asthma experience in their day-to-day lives (102)	The Pediatric Asthma Quality of Life Questionnaire (PAQLQ) is one of the most widely used instruments for measuring health-related QoL in children with asthma. The standardized version of PAQLQ contains 23 questions in three domains, i.e., activity limitation, symptoms and emotional function .

Outcome measure	Definition	Validity	Clinical relevance
Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ)	Paediatric Rhinoconjunctivitis Quality of Life Questionnaire	(103)	The PRQLQ has 23 items in five domains (nose symptoms, eye symptoms, practical problems, other symptoms, and activities)
AEs	Adverse events can include any unfavourableClick or tap here to enter text. and/or unintended signs, abnormal laboratory tests, imaging analysis or other findings associated with the treatment. Adverse events may be expected or unexpected.	AEs as outcome measure are used in most studies evaluation safety of a the treatment of interest.	To investigate the safety profile of dupilumab compared to other comparators in the treatment of asthma with different characteristics.
SAE	Any untoward medical occurrence that at any dose. Results in death. Is life-threatening. Requires inpatient hospitalization or causes prolongation of existing hospitalization.	Used in prior DMC submission for asthma and for treatment guideline protocol (19, 50)	The minimal clinically important difference for treatment discontinuations due to AEs is 5%-point (19, 50)

Results per study

Severe allergic asthma

Table 94. Results of Liberty Asthma VOYAGE (NCT02948959) Severe Allergic Asthma

Results of Liberty Asthma VOYAGE (NCT02948959) for severe allergic asthma				
	Estimated absolute difference in effect	**Estimated relative difference in effect**	**Description of methods used for estimation**	**References**

Results of Liberty Asthma VOYAGE (NCT02948959) for severe allergic asthma

Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Annualized rate of severe asthma exacerbations during 52-week treatment period	Dupilumab	115	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	The annualized rate of severe exacerbation events was analyzed using a negative binominal regression model that includes the total number of events observed from randomization up to week 52 or last study contact date (whichever comes earlier) as the response variable, and includes treatment group, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, and number of severe exacerbation events within 1 year prior to the study as covariates, and log-transformed standardized observation duration as an offset variable.	(24)
	Placebo	63	[redacted]								
% experience no exacerbation during 52-week treatment periods, %	Dupilumab	115	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	All severe exacerbation events occurred during the 52-week treatment period are included, regardless of whether the patient is on-treatment or not	(24)
	Placebo	63	[redacted]								
Change from BL at week 12 of ppFEV1, (±SE)	Dupilumab	115	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Change from baseline in percentage of predicted FEV1 was analyzed using a mixed-effect model with repeated measures approach, including treatment, baseline weight, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment-by-visit interaction, baseline percentage of predicted FEV1 value, and baseline-by-visit interaction as covariates.	(24)
	Placebo	63	[redacted]								

Results of Liberty Asthma VOYAGE (NCT02948959) for severe allergic asthma													
% patients with >=200mL improvement in FEV1 at week 12 (95% CI)	Dupilumab	115	[redacted]									Patients with missing pre-bronchodilator FEV1 at W12 were considered as no improvement.	(24)
	Placebo	63	[redacted]										
Change from BL in ACQ-7-IA, (±SE)	Dupilumab	115	[redacted]									Derived from MMRM model with change from baseline in ACQ-7-IA up to Week 24 as the response variable, and treatment, age, weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline ACQ-7-IA and baseline-by-visit interaction as covariates.	(24)
	Placebo	63	[redacted]										
Change from BL at week 52 of PAQLQ-IA global score	Dupilumab	115	[redacted]									Derived from MMRM model with change from baseline in PRQLQ global score values up to Week 52 as the response variable, and treatment, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline PRQLQ global score and baseline-by-visit interaction as covariates.	(27)
	Placebo	63	[redacted]										
Change from BL at week 52 of PRQLQ	Dupilumab	115	[redacted]									Derived from MMRM model with change from baseline in PAQLQ(S)-IA global score values up to Week 52 as the response variable, and treatment, age, baseline weight group, region, baseline eosinophil level,	(27)
	Placebo	63	[redacted]										

Results of Liberty Asthma VOYAGE (NCT02948959) for severe allergic asthma											
global score (+SE)										baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline PAQLQ(S)-IA global score and baseline-by-visit interaction as covariates.	
AE, n (%)	Dupilumab	271	225 (83.0)	3.18%	(-4.96% - 11.31%)	NA	1.04	(0.94 - 1.15)	0.4565	The safety variables, including TEAEs, laboratory parameters, vital signs, ECG, and physical examinations will be summarized using descriptive statistics.	(27)
	Placebo	134	107 (79.9)								
SAE, n (%)	Dupilumab	271	13 (4.8)	0.32%	(-4.01% - 4.65%)	NA	1.07	(0.42 - 2.76)	0.8950		(27)
	Placebo	134	6 (4.5)								
AEs leading to discontinuation, n (%)	Dupilumab	271	5 (1.8)	0.35%	(-2.25% - 2.96%)	NA	1.24	(0.24 - 6.29)	0.8103		(27)
	Placebo	134	2 (1.5)								

Table 95. Results of IA05 (Kulus et al., 2010) (NCT00079937) for severe allergic asthma

Results of OMALIZUMAB (NCT00079937) for severe allergic asthma											
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	Omalizumab	159	0.42 (NA)	21.02	7.72 - 34.31	0.002	RR: 0.662	0.441, 0.995	0.047		(16)

Results of OMALIZUMAB (NCT00079937) for severe allergic asthma											
Clinically significant asthma exacerbation rate, week 0-24	Placebo	76	0.63 (NA)							Statistical differences between group baseline characteristics were tested using the F-test, chi-squared test and Fisher's exact test, as appropriate. Rate of clinically significant asthma exacerbations over 24 and 52 weeks were compared between treatment groups using a two-sided test at a=0.05 with a generalized Poisson regression model. The rate ratio (RR) of exacerbations between the treatment groups and 95% confidence interval (CI) were obtained.	
Clinically significant asthma exacerbation rate, week 0-52	Omalizumab	159	0.73 (NA)	0.71	0.59-0.83	<0.001	RR: 0.504	0.350, 0.725	<0.001	Statistical differences between group baseline characteristics were tested using the F-test, chi-squared test and Fisher's exact test, as appropriate. Rate of clinically significant asthma exacerbations over 24 and 52 weeks were compared between treatment groups using a two-sided test at a=0.05 with a generalized Poisson regression model. The rate ratio (RR) of exacerbations between the treatment groups and 95% confidence interval (CI) were obtained.	(16)
	Placebo	76	1.44 (NA)								
% reduction in ICS dose during the steroid-adjustable phase	Omalizumab	159	2.5 (NA)	0.5	NA	NA	NA	NA	NA	The percentage change from baseline in ICS dose was compared using the van Elteren test: a nonparametric test that compares treatments in the presence of blocking (an extension of Wilcoxon's rank-sum test)41; percent change in ICS dose for patients who discontinued before the 28-	(16)
	Placebo	76	2.0 (NA)								

Results of OMALIZUMAB (NCT00079937) for severe allergic asthma											
										week adjustable-steroid phase was imputed as zero.	
Clinically significant asthma exacerbation rate, week 25-52	Omalizumab	159	0.29 (NA)	-0.48	-0.60, -0.36	<0.001 NA	RR: 0.372	0.243, 0.568	<0.001	Statistical differences between group baseline characteristics were tested using the F-test, chi-squared test and Fisher's exact test, as appropriate. Rate of clinically significant asthma exacerbations over 24 and 52 weeks were compared between treatment groups using a two-sided test at a=0.05 with a generalized Poisson regression model. The rate ratio (RR) of exacerbations between the treatment groups and 95% confidence interval (CI) were obtained.	(16)
	Placebo	76	0.77 (NA)								
Rate of clinically significant exacerbations over 52 weeks in patients with baseline percent predicted FEV1 <80%	Omalizumab	61	0.84 (NA)	-0.8	-0.96, -0.64	<0.001	RR: 0.512	0.315, 0.833	0.007	Statistical differences between group baseline characteristics were tested using the F-test, chi-squared test and Fisher's exact test, as appropriate. Rate of clinically significant asthma exacerbations over 24 and 52 weeks were compared between treatment groups using a two-sided test at a=0.05 with a generalized Poisson regression model. The rate ratio (RR) of exacerbations between the treatment groups and 95% confidence interval (CI) were obtained.	(16)
	Placebo	28	1.64 (NA)								
Rate of clinically significant	Omalizumab	54	0.66 (NA)	-0.69	-0.79, -0.59	<0.001	RR: 0.455	0.279, 0.854	0.012	Statistical differences between group baseline characteristics were tested using the F-test, chi-squared test and	
	Placebo	35	1.35 (NA)								

Results of OMALIZUMAB (NCT00079937) for severe allergic asthma										
exacerbations over 52 weeks in patients with baseline percent predicted FEV1 ≥80%									Fisher's exact test, as appropriate. Rate of clinically significant asthma exacerbations over 24 and 52 weeks were compared between treatment groups using a two-sided test at a=0.05 with a generalized Poisson regression model. The rate ratio (RR) of exacerbations between the treatment groups and 95% confidence interval (CI) were obtained.	
AE, n (%)	Omalizumab	166	155 (93.4)	-1.6	-7.72; - 4.47	0.779	0.98	0.92 - 1.05	0.6125	Assessment of safety was based on the frequency of all AEs. Statistical differences between the frequency of AEs reported in the omalizumab and placebo groups were calculated using Fisher's exact test	(25)
	Placebo	80	76 (95.0)								
SAE, n (%)	Omalizumab	166	2 (1.2)	1.20%	-0.45% - 2.86%)	0.1553	2.42	0.12 – 49.77	0.5791	Assessment of safety was based on the frequency of all AEs. Statistical differences between the frequency of AEs reported in the omalizumab and placebo groups were calculated using Fisher's exact test 0.5 added to all cells in 2x2, to calculate relative differences as 0 events occurred in placebo arm.	(16)
	Placebo	80	0 (0)								
Discontinued due to AE, n (%)	Omalizumab	166	6 (3.6)	-6.39	(-13.55; 0.78)	0.0801	0.36	(0.13 - 1.01)	0.0511	Assessment of safety was based on the frequency of all AEs. Statistical differences between the frequency of AEs reported in the omalizumab and placebo	(16)
	Placebo	80	8 (10.0)								

Results of OMALIZUMAB (NCT00079937) for severe allergic asthma	
	groups were calculated using Fisher's exact test

Table 96. Results of Lanier et al., 2009 (NCT00079937) for severe allergic asthma(15)

Results of Omalizumab (NCT00079937) for severe allergic asthma											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Change from BL at week 24 of PAQLQ-IA global score*	Omalizumab	NA	NA	0.04	NA	0.676	NA	NA	NA	*PAQLQ overall score was compared by using an analysis of covariance; missing data were imputed by using the last available assessments.* *The level of statistical significance was adjusted for secondary efficacy endpoints, based on the hierarchical Hochberg multiple testing procedure*	(15)
	Placebo	NA	NA								

Severe eosinophilic asthma

Table 97. Results of Liberty Asthma VOYAGE (NCT02948959) for severe eosinophilic asthma

Results of Liberty Asthma VOYAGE (NCT02948959) for severe eosinophilic asthma											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Annualized rate of severe asthma exacerbations during 52-week treatment period	Dupilumab	212	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	The annualized rate of severe exacerbation events was analyzed using a negative binominal regression model that includes the total number of events observed from randomization up to week 52 or last study contact date (whichever comes earlier) as the response variable, and includes treatment group, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, and number of severe exacerbation events within 1 year prior to the study as covariates, and log-transformed standardized observation duration as an offset variable.	(24)
	Placebo	107	[redacted]								
% experience no exacerbation during 52-week treatment periods, %	Dupilumab	212	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	All severe exacerbation events occurred during the 52-week treatment period are included, regardless of whether the patient is on-treatment or not OR, RR and RD are derived from a logistic regression model with treatment, age, weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, and number of severe exacerbation events within 1 year prior to the study as covariates.	(24)
	Placebo	107	[redacted]								
	Dupilumab	212	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Change from baseline in percentage of predicted FEV1 was analyzed using a	(24)

Results of Liberty Asthma VOYAGE (NCT02948959) for severe eosinophilic asthma														
Change from BL at week 12 of ppFEV1, (±SE)	Placebo	107	[redacted]										mixed-effect model with repeated measures approach, including treatment, baseline weight, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment-by-visit interaction, baseline percentage of predicted FEV1 value, and baseline-by-visit interaction as covariates.	
% patients with >=200mL improvement in FEV1 at week 12 (95% CI)	Dupilumab	212	[redacted]										RR and RD are derived from a logistic regression model with treatment, age, weight group, region, baseline eosinophil level, baseline ICS dose level, and baseline pre-bronchodilator FEV1 as covariates. Patients with missing pre-bronchodilator FEV1 at W12 were considered as no improvement.	(24)
	Placebo	107	[redacted]											
Change from BL in ACQ-7-IA, (±SE)	Dupilumab	212	[redacted]										Derived from MMRM model with change from baseline in ACQ-7-IA up to Week 24 as the response variable, and treatment, age, weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline ACQ-7-IA and baseline-by-visit interaction as covariates.	(24)
	Placebo	107	[redacted]											
Change from BL at week 52 of PAQLQ-IA global score	Dupilumab	212	[redacted]										Derived from MMRM model with change from baseline in PAQLQ(S)-IA global score values up to Week 52 as the response variable, and treatment, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline PAQLQ(S)-IA global score and baseline-by-visit interaction as covariates.	(27)
	Placebo	107	[redacted]											

Results of Liberty Asthma VOYAGE (NCT02948959) for severe eosinophilic asthma											
Change from BL at week 52 of PRQLQ global score (+SE)	Dupilumab	212	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Derived from MMRM model with change from baseline in PAQLQ(S)-IA global score values up to Week 52 as the response variable, and treatment, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline PAQLQ(S)-IA global score and baseline-by-visit interaction as covariates.	(27)
	Placebo	107	[redacted]								
AE, n (%)	Dupilumab	271	225 (83.0)	3.18%	(-4.96% - 11.31%)	NA	1.04	(0.94 - 1.15)	0.4565	The safety variables, including AEs, laboratory parameters, vital signs, ECG, and physical examinations will be summarized using descriptive statistics.	(27)
	Placebo	134	107 (79.9)								
SAE, n (%)	Dupilumab	271	13 (4.8)	0.32%	(-4.01% - 4.65%)	NA	1.07	(0.42 - 2.76)	0.8950		(27)
	Placebo	134	6 (4.5)								
AEs leading to discontinuation, n (%)	Dupilumab	271	5 (1.8)	0.35%	(-2.25% - 2.96%)	NA	1.24	(0.24 - 6.29)	0.8103		(27)
	Placebo	134	2 (1.5)								

Table 98. Results of MEPOLIZUMAB (NCT02377427) for severe eosinophilic asthma

Results of MEPOLIZUMAB (NCT02377427) for severe eosinophilic asthma											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		

Results of MEPOLIZUMAB (NCT02377427) for severe eosinophilic asthma											
$AUC_{(0\text{-}inf)}$ (µg · day/mL)	Mepolizumab 40mg	26	454.4 (422.1, 486.7)	NA	NA	NA	NA	NA	NA	*Mepolizumab plasma PK concentrations were analyzed by nonlinear mixed-effect modeling methods (SAS Institute Inc, Cary, NC). A two-compartment model with first-order absorption and elimination was used with PK distribution parameters and bioavailability fixed to previously estimated adult values. Bodyweight was incorporated into the model using physiological allometry with allometric exponents for clearance and volumes estimated. Final model appropriateness was assessed using goodness of fit plots, simulations, and statistical test*	(18)
	Mepolizumab 100mg	10	675.2 (602.2, 748.2)								
	Mepolizumab 40/100mg	NA	NA								
C_{max} (µg/mL)	Mepolizumab 40mg	26	10.2 (9.5, 10.9)	NA	NA	NA	NA	NA	NA	*Mepolizumab plasma PK concentrations were analyzed by nonlinear mixed-effect modeling methods (SAS Institute Inc, Cary, NC). A two-compartment model with first-order absorption and elimination was used with PK distribution parameters and bioavailability fixed to previously estimated adult values. Bodyweight was incorporated into the model using physiological allometry with allometric exponents for clearance and volumes estimated. Final model appropriateness was assessed using goodness of fit plots, simulations, and statistical test*	(18)
	Mepolizumab 100mg	10	16.3 (15.0, 17.6)								
	Mepolizumab 40/100mg	NA	NA								
$C_{max\ SS}$ (µg/mL)	Mepolizumab 40mg	26	17.8 (15.3, 20.2)	NA	NA	NA	NA	NA	NA	*Mepolizumab plasma PK concentrations were analyzed by nonlinear mixed-effect modeling methods (SAS Institute Inc, Cary, NC). A two-compartment model with first-order absorption and elimination was used with PK distribution parameters and bioavailability fixed to previously estimated adult values. Bodyweight was incorporated into the model using physiological allometry with allometric exponents for clearance and volumes estimated. Final model appropriateness was*	(18)
	Mepolizumab 100mg	10	28.5 (25.0, 31.9)								
	Mepolizumab 40/100mg	NA	NA								

Results of MEPOLIZUMAB (NCT02377427) for severe eosinophilic asthma											
										assessed using goodness of fit plots, simulations, and statistical test	
CL/F (L/day)	Mepolizumab 40mg	26	0.09 (0.08, 0.09)	NA	NA	NA	NA	NA	NA	*Mepolizumab plasma PK concentrations were analyzed by nonlinear mixed-effect modeling methods (SAS Institute Inc, Cary, NC). A two-compartment model with first-order absorption and elimination was used with PK distribution parameters and bioavailability fixed to previously estimated adult values. Bodyweight was incorporated into the model using physiological allometry with allometric exponents for clearance and volumes estimated. Final model appropriateness was assessed using goodness of fit plots, simulations, and statistical test*	(18)
	Mepolizumab 100mg	10	0.15 (0.13, 0.16)								
	Mepolizumab 40/100mg	NA	NA								
C_{av} *(µg/mL)*	Mepolizumab 40mg	26	16.2 (15.1, 17.4)	NA	NA	NA	NA	NA	NA	*Mepolizumab plasma PK concentrations were analyzed by nonlinear mixed-effect modeling methods (SAS Institute Inc, Cary, NC). A two-compartment model with first-order absorption and elimination was used with PK distribution parameters and bioavailability fixed to previously estimated adult values. Bodyweight was incorporated into the model using physiological allometry with allometric exponents for clearance and volumes estimated. Final model appropriateness was assessed using goodness of fit plots, simulations, and statistical test*	(18)
	Mepolizumab 100mg	10	24.1 (21.5, 26.7)								
	Mepolizumab 40/100mg	NA	NA								
$t_{½}$ *(days)*	Mepolizumab 40mg	26	23.6 (21.9, 25.3)	NA	NA	NA	NA	NA	NA	*Mepolizumab plasma PK concentrations were analyzed by nonlinear mixed-effect modeling methods (SAS Institute Inc, Cary, NC). A two-compartment model with first-order absorption and elimination was used with PK distribution parameters and bioavailability fixed to previously estimated adult values. Bodyweight was incorporated into the model using physiological allometry with allometric exponents for clearance and volumes*	(26)
	Mepolizumab 100mg	10	21.8 (19.6, 24.1)								
	Mepolizumab 40/100mg	NA	NA								

Results of MEPOLIZUMAB (NCT02377427) for severe eosinophilic asthma											
										estimated. Final model appropriateness was assessed using goodness of fit plots, simulations, and statistical test	
Blood eosinophil count, cells/µL, week 12/ % reduction from BL at week 12	Mepolizumab 40mg	26	42 (26, 67)/ 88.5%	NA	NA	NA	NA	NA	NA	*The ratio of blood eosinophil count at week 12 to baseline was summarized descriptively, and the ratio at each visit to baseline presented graphically. Bodyweight-adjusted apparent clearance point estimates with 90% CIs in children 6 to 11 years were presented alongside the historical estimated adult value of 0.29 L/day (unpublished data) with a proposed 80% to 125% interval around this estimate of 0.23 to 0.36 L/day*	(26)
	Mepolizumab 100mg	10	55 (31, 97)/ 83.4%								
	Mepolizumab 40/100mg	NA	NA								
ACQ-7	Mepolizumab 40mg	26	-0.55 (-1.01, -0.09)[a] -0.65 (-1.15, -1.16)[b] -0.41 (-0.91, 0.08)[c] 11/23 (48%)[d]	NA	NA	NA	NA	NA	NA	*For blood eosinophil counts and asthma control questionnaire scores, baseline was defined as the value recorded before the first mepolizumab treatment in part A (overall study week 0). All statistical analyses were performed with SAS software (version 9.4; SAS Institute, Cary, NC)*	(26)
	Mepolizumab 100mg	10	-0.47 (-1.16, 0.21)[a] -0.30(-1.19, 0.59)[b] 0.08 (-0.88, 1.04)[c]								

Results of MEPOLIZUMAB (NCT02377427) for severe eosinophilic asthma											
			5/10 (50%)[d]								
	Mepolizumab 40/100mg	NA	NA								
C-ACT	Mepolizumab 40mg	26	1.8 (0.2, 3.5)[a] 3.0 (0.7, 5.4)[b] 2.1 (0.2, 4.1)[c]	NA	NA	NA	NA	NA	NA	*For blood eosinophil counts and asthma control questionnaire scores, baseline was defined as the value recorded before the first mepolizumab treatment in part A (overall study week 0). All statistical analyses were performed with SAS software (version 9.4; SAS Institute, Cary, NC)*	(26)
	Mepolizumab 100mg	10	2.4 (-0.9, 5.7)[a] 1.5 (-1.6, 4.6)[b] -0.3 (-4.0, 3.4)[c]								
	Mepolizumab 40/100mg	NA	NA								
Prebronchodilator FEV_1 (mL)	Mepolizumab 40mg	26	93 (-19, 206)[a] 90 (-17, 198)[b] 72 (-37, 181)[c]	NA	NA	NA	NA	NA	NA	*NA*	(26)
	Mepolizumab 100mg	10	55 (-52, 162)[a] -63 (-314, 188)[b] 2 (-175, 179)[c]								
	Mepolizumab 40/100mg	NA	NA								
Patients with on-	Mepolizumab 40mg	26	8 (31)[e] 6 (23)[f]	NA	NA	NA	NA	NA	NA	*NA*	(26)

Results of MEPOLIZUMAB (NCT02377427) for severe eosinophilic asthma											
treatment exacerbations (week 0-12), n (%)			2 (8)[g]								
	Mepolizumab 100mg	10	2 (20)[e] 1 (10)[f] 1 (10)[g]								
	Mepolizumab 40/100mg	NA	NA								
Serum total IL-5 levels, ng/L	Mepolizumab 40mg	26	137.1 (NA)	NA	NA	NA	NA	NA	NA	*NA*	(26)
	Mepolizumab 100mg	10	96.4 (NA)								
	Mepolizumab 40/100mg	NA	NA								
AE, n(%)	Mepolizumab 40mg	16	15 (94)	NA	NA	NA	NA	NA	NA	*All statistical analyses were performed by using the safety population (all children who received ≥1 dose of mepolizumab within part B). Endpoints were summarized by using appropriate descriptive statistics (mean/geometric mean, median, SD, and range). AEs were summarized by using the Medical Dictionary for Regulatory Activities Primary System Organ Class and Preferred Terms. Annualized exacerbation rates were determined by using a negative binomial generalized linear model with logarithm of time as an offset variable, from which estimated rates per year and 95% CIs were calculated.*	(51)
	Mepolizumab 100mg	10	8 (80)								
	Mepolizumab 40/100mg	4	4 (100)								
Treatment-	Mepolizumab 40mg	16	4 (25)	NA	NA	NA	NA	NA	NA	*All statistical analyses were performed by using the safety population (all children who received ≥1 dose of mepolizumab*	(51)

Results of MEPOLIZUMAB (NCT02377427) for severe eosinophilic asthma											
related on-treatment AEs	Mepolizumab 100mg	10	3 (3)							*within part B). Endpoints were summarized by using appropriate descriptive statistics (mean/geometric mean, median, SD, and range). AEs were summarized by using the Medical Dictionary for Regulatory Activities Primary System Organ Class and Preferred Terms. Annualized exacerbation rates were determined by using a negative binomial generalized linear model with logarithm of time as an offset variable, from which estimated rates per year and 95% CIs were calculated.*	
	Mepolizumab 40/100mg	4	1 (25)								
AE leading to discontinuation of treatment	Mepolizumab 40mg	16	0	NA	NA	NA	NA	NA	NA	*All statistical analyses were performed by using the safety population (all children who received ≥1 dose of mepolizumab within part B). Endpoints were summarized by using appropriate descriptive statistics (mean/geometric mean, median, SD, and range). AEs were summarized by using the Medical Dictionary for Regulatory Activities Primary System Organ Class and Preferred Terms. Annualized exacerbation rates were determined by using a negative binomial generalized linear model with logarithm of time as an offset variable, from which estimated rates per year and 95% CIs were calculated.*	(51)
	Mepolizumab 100mg	10	0								
	Mepolizumab 40/100mg	4	0								
SAE, n (%)	Mepolizumab 40mg	16	5 (31)	NA	NA	NA	NA	NA	NA	*All statistical analyses were performed by using the safety population (all children who received ≥1 dose of mepolizumab within part B). Endpoints were summarized by using appropriate descriptive statistics (mean/geometric mean, median, SD, and range). AEs were summarized by using the Medical Dictionary for Regulatory Activities Primary System Organ Class and Preferred Terms. Annualized exacerbation rates were determined by using a negative binomial generalized linear model with logarithm of time as an offset*	(51)
	Mepolizumab 100mg	10	3 (30)								
	Mepolizumab 40/100mg	4	1 (25)								

Results of MEPOLIZUMAB (NCT02377427) for severe eosinophilic asthma											
										variable, from which estimated rates per year and 95% CIs were calculated.	
Blood eosinophil count, cells/µL, geometric mean (SD log), week 52	Mepolizumab 40mg	16	48 (0.858)	NA	NA	NA	NA	NA	NA	*For blood eosinophil counts, the ratio to baseline was summarized by visit; if a result of zero was recorded, a small value (half the minimum nonzero result) was imputed before log-transformation. For blood eosinophil counts and asthma control questionnaire scores, baseline was defined as the value recorded before the first mepolizumab treatment in part A (overall study week 0). All statistical analyses were performed with SAS software (version 9.4; SAS Institute, Cary, NC)*	(51)
	Mepolizumab 100mg	10	44 (1.022)								
	Mepolizumab 40/100mg	4	47 (0.841)								

[a] Change from BL at week 4, [b] Change from BL at week 8, [c] Change from BL at week 12, [d] ≥0.5 point reduction from BL, n/N (%), [e] Any on treatment exacerbation, [f] 1 exacerbation, [g] 2 exacerbations

Severe asthma with elevated FeNO

Table 99. Results of Liberty Asthma VOYAGE (NCT02948959) for severe asthma with elevated FeNO

Results of Liberty Asthma VOYAGE (NCT02948959) for severe asthma with elevated FeNO											
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Annualized rate of severe asthma exacerbations	Dupilumab	254	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	The annualized rate of severe exacerbation events was analyzed using a negative binominal regression model that includes the total number of events observed from randomization up to week 52 or last study contact date (whichever comes earlier) as the response variable, and includes treatment group, age, baseline weight group, region, baseline eosinophil level, baseline	(24)
	Placebo	130	[redacted]								

Results of Liberty Asthma VOYAGE (NCT02948959) for severe asthma with elevated FeNO														
during 52-week treatment period													FeNO level, baseline ICS dose level, and number of severe exacerbation events within 1 year prior to the study as covariates, and log-transformed standardized observation duration as an offset variable.	
% experience no exacerbation during 52-week treatment periods, %	Dupilumab	254	[redacted]										The change from baseline for continuous endpoints was analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model included change from baseline as response variables, and for treatment, age, weight (≤30kg, >30kg), region, baseline eosinophil level (<150 cells/µL, 50 – 299 cells/µL, and ≥300 cells/µL), ICS (medium/high) strata, visit, treatment-by-visit interaction, baseline value, and baseline-by-visit interaction as covariates. Sex, height, and ethnicity was also included as covariates in the models for spirometry parameters. An unstructured correlation matrix was used to model the within-patient errors. Parameters was estimated using restricted maximum likelihood method using the Newton-Raphson algorithm. Statistical inferences on treatment comparisons for the change in percentage from baseline at Weeks 12 was derived from the mixed-effect model with Kenward and Roger degree of freedom a justment approach.	(24)
	Placebo	130	[redacted]											
Change from BL at week 12 of ppFEV1, (±SE)	Dupilumab	254	[redacted]										Change from baseline in percentage of predicted FEV1 was analyzed using a mixed-effect model with repeated measures approach, including treatment, baseline weight, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment-by-visit interaction, baseline percentage of predicted FEV1 value, and baseline-by-visit interaction as covariates.	(24)
	Placebo	130	[redacted]											

Results of Liberty Asthma VOYAGE (NCT02948959) for severe asthma with elevated FeNO												
% patients with >=200mL improvement in FEV1 at week 12 (95% CI)	Dupilumab	254	[redacted]								RR and RD are derived from a logistic regression model with treatment, age, weight group, region, baseline eosinophil level, baseline ICS dose level, and baseline pre-bronchodilator FEV1 as covariates. Patients with missing pre-bronchodilator FEV1 at W12 were considered as no improvement.	(24)
	Placebo	130	[redacted]									
Change from BL in ACQ-7-IA, (±SE)	Dupilumab	254	[redacted]								Derived from MMRM model with change from baseline in ACQ-7-IA up to Week 24 as the response variable, and treatment, age, weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline ACQ-7-IA and baseline-by-visit interaction as covariates.	(24)
	Placebo	130	[redacted]									
Change from BL at week 52 of PAQLQ-IA global score	Dupilumab	254	[redacted]								Derived from MMRM model with change from baseline in PAQLQ(S)-IA global score values up to Week 52 as the response variable, and treatment, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline PAQLQ(S)-IA global score and baseline-by-visit interaction as covariates.	(27)
	Placebo	130	[redacted]									
Change from BL at week 52 of PRQLQ	Dupilumab	254	[redacted]								Derived from MMRM model with change from baseline in PAQLQ(S)-IA global score values up to Week 52 as the response variable, and treatment, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction,	(27)
	Placebo	130	[redacted]									

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Results of Liberty Asthma VOYAGE (NCT02948959) for severe asthma with elevated FeNO											
global score (+SE)										baseline PAQLQ(S)-IA global score and baseline-by-visit interaction as covariates.	
AE, n (%)	Dupilumab	271	225 (83.0)	3.18%	(-4.96% - 11.31%)	NA	1.04	(0.94 - 1.15)	0.4565	The safety variables, including AEs, laboratory parameters, vital signs, ECG, and physical examinations will be summarized using descriptive statistics.	(27)
	Placebo	134	107 (79.9)								
SAE, n (%)	Dupilumab	271	13 (4.8)	0.32%	(-4.01% - 4.65%)	NA	1.07	(0.42 - 2.76)	0.8950		(27)
	Placebo	134	6 (4.5)								
AEs leading to discontinuation, n (%)	Dupilumab	271	5 (1.8)	0.35%	(-2.25% - 2.96%)	NA	1.24	(0.24 - 6.29)	0.8103		(27)
	Placebo	134	2 (1.5)								

Non-allergic asthma with high EOS or high FeNO

Table 100 Non-allergic asthma with high EOS or high FeNO

Results of Liberty Asthma VOYAGE (NCT02948959) for non-allergic asthma with high EOS or high FeNO											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Annualized rate of	Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	All severe exacerbation events occurred during the 52-week treatment period are	(24)

Results of Liberty Asthma VOYAGE (NCT02948959) for non-allergic asthma with high EOS or high FeNO

severe asthma exacerbations during 52-week treatment period	Placebo	[redacted]	[redacted]							included, regardless of whether the patient is on-treatment or not The total number of events that occurred during the 52-week treatment period divided by the total number of patient-years followed in the 52-week treatment period. Derived using negative binomial model with the total number of events onset from randomization up to Week 52 visit or last contact date (whichever comes earlier) as the response variable, with the treatment group, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study as covariates, and log-transformed standardized observation duration as an offset variable.	
% experience no exacerbation during 52-week treatment periods, %	Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	All severe exacerbation events occurred during the 52-week treatment period are included, regardless of whether the patient is on-treatment or not OR, RR and RD are derived from a logistic regression model with treatment, age, weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, and number of severe exacerbation events within 1 year prior to the study as covariates	(24)
	Placebo	[redacted]	[redacted]								
Change from BL at week 12 of ppFEV1, (±SE)	Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Derived from MMRM model with change from baseline in Pre-bronchodilator % predicted FEV1 values up to Week 12 as the response variable, and treatment, baseline weight group, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline Pre-bronchodilator % predicted FEV1 value	(24)
	Placebo	[redacted]	[redacted]								

Results of Liberty Asthma VOYAGE (NCT02948959) for non-allergic asthma with high EOS or high FeNO											
										and baseline-by-visit interaction as co-variates	
% patients with >=200mL improve-ment in FEV1 at week 12 (95% CI)	Dupilumab	[redacted]								RR and RD are derived from a logistic re-gression model with treatment, age, weight group, region, baseline eosinophil level, baseline ICS dose level, and base-line pre-bronchodilator FEV1 as covari-ates. Patients with missing pre-bronchodilator FEV1 at W12 were considered as no im-provement.	(24)
	Placebo	[redacted]									
Change from BL in ACQ-7-IA, (±SE)	Dupilumab	[redacted]								Derived from MMRM model with change from baseline in ACQ-7-IA up to Week 24 as the response variable, and treatment, age, weight group, region, baseline eosin-ophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit in-teraction, baseline ACQ-7-IA and base-line-by-visit interaction as covariates.	(24)
	Placebo	[redacted]									
Change from BL at week 52 of PAQLQ-IA global score	Dupilumab	[redacted]								Derived from MMRM model with change from baseline in PAQLQ(S)-IA global score values up to Week 52 as the response vari-able, and treatment, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline PAQLQ(S)-IA global score and baseline-by-visit interaction as covariates.	(27)
	Placebo	[redacted]									
Change from BL at week 52 of PRQLQ	Dupilumab	[redacted]								Derived from MMRM model with change from baseline in PAQLQ(S)-IA global score values up to Week 52 as the response vari-able, and treatment, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction,	(27)
	Placebo	[redacted]									

Results of Liberty Asthma VOYAGE (NCT02948959) for non-allergic asthma with high EOS or high FeNO											
global score (+SE)										baseline PAQLQ(S)-IA global score and baseline-by-visit interaction as covariates.	
AE, n (%)	Dupilumab	271	225 (83.0)	3.18%	(-4.96% - 11.31%)	NA	1.04	(0.94 - 1.15)	0.4565	The safety variables, including AEs, laboratory parameters, vital signs, ECG, and physical examinations will be summarized using descriptive statistics.	(27)
	Placebo	134	107 (79.9)								
SAE, n (%)	Dupilumab	271	13 (4.8)	0.32%	(-4.01% - 4.65%)	NA	1.07	(0.42 - 2.76)	0.8950		(27)
	Placebo	134	6 (4.5)								
AEs leading to discontinuation, n (%)	Dupilumab	271	5 (1.8)	0.35%	(-2.25% - 2.96%)	NA	1.24	(0.24 - 6.29)	0.8103		(27)
	Placebo	134	2 (1.5)								

Appendix E Safety data for intervention and comparator(s)

See section 0 for all safety data for intervention and comparators.

Additional table regarding treatment emergent adverse events leading to permanent treatment discontinuation:

Table 101. [redacted]

[redacted]

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Appendix F Comparative analysis of efficacy and safety

Ultimately, a total of three trials were assessed for patient characteristics one evaluating treatment with dupilumab [VOYAGE; NCT02948959], and two other consisting of omalizumab trials [IA05: NCT00079937 and ICATA: NCT00377572]) were assessed for patient characteristics wherein major differences were observed with regards to key characteristics, including the presence of allergic phenotype via a positive skin prick test or a positive in vitro response to ≥1 perennial allergen in the omalizumab trials, and differences in baseline EOS, ppFEV1, and prior exacerbations and lack of reporting was observed for ICATA (Table 102). These differences were believed to be a potential source of bias to the ITC; hence the main analyses were presented narratively.

In order to account for any potential bias that differences in patient characteristics may cause, a subgroup of patients from VOYAGE was derived via post hoc analyses. The 'omalizumab-eligible' subgroup attempted to better align patients from VOYAGE with those in the IA05 trial, based on an allergic phenotype and corresponding to the inclusion criteria of IA05, which was defined by:

- Baseline weight between 20-150 kg and serum IgE level of 30 to 1300 IU/mL and weight-IgE values combinations based on omalizumab dosing table
- At least 1 positive perennial allergen-specific IgE (concentration >=0.35 IU/mL) among the following allergens: Alternaria tenuis/alternata; Cladosporium herbarum/hormodendrum; Aspergillus Fumigatus; Cat Dander; D. Farinae; D. Pteronyssinus; Dog Dander; German Cockroach

It should be noted that the allergic phenotype in IA05 was based on skin prick test or a positive in vitro response to ≥1 perennial allergen. These tests were not performed as part of the VOYAGE trial, and therefore the presence of 1 positive perennial allergen-specific IgE was used as a proxy for the allergic phenotype in IA05.

In attempt to account for differences in the definition of severe exacerbations that may lead to bias, a similar approach was used, wherein post hoc analyses of VOYAGE were carried out. The modified definition from VOYAGE (deterioration of asthma) was validated by clinical experts as being more comparable to primary exacerbation outcome in IA05 defined as "clinically significant asthma exacerbations." The caveat was that VOYAGE did not allow for doubling of ICS, as permitted in IA05. The outcome definitions, observed placebo rates, and annualized RRs are presented in presented in Table 103.

In summary, two studies (VOYAGE and IA05) were deemed appropriate for the exploratory ITCs, and the inclusion of one additional study (ICATA) was explored for severe exacerbations, which was the only commonly reported outcome from this trial for patients age 6-11 years. The network of connected trials suitable for ITC is displayed in Figure 20. Analyses of severe exacerbations excluding the ICATA3 trial were performed given the limited reporting of baseline characteristics and differences in the study design and population in ICATA.

Table 102 Patient Characteristics of Trials and Subgroups included in the ITCs

Trial Name	Treatment Arm	N	Age, [Range] Mean (SD)	Age, Mean (SD), Range	Male, %	White, %	Baseline EOS (Cells/uL), Mean (SD)	Baseline FeNO, Mean (SD)	Exacerbations in Previous Year, Mean (SD)	Baseline IgE, Mean (SD)	$ppFEV_1$, Mean (SD)
VOYAGE ITT[1]	Dupilumab 100-200 mg Q2W										
	Placebo										
VOYAGE Omalizumab-eligible	Dupilumab 100-200 mg Q2W										
	Placebo										
IA05[210] ITT	Omalizumab 75-375mg Q1M/Q2M										
	Placebo										

Abbreviations: EOS = eosinophil; FeNO = fractional exhaled nitric oxide; IgE = immunoglobulin E; ppFEV1 = percent predicted forced expiratory volume in one second; Q1M = once a month; Q2M = twice a month; Q2W = every two weeks; SD = standard deviation

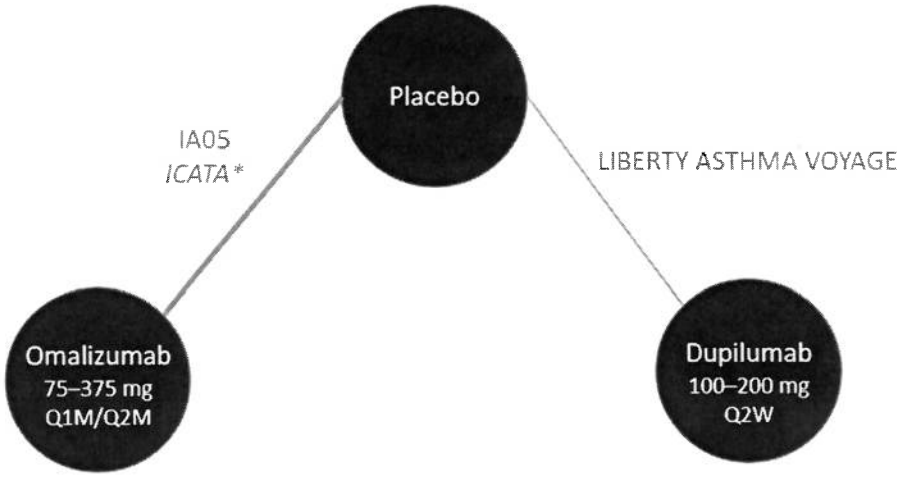
Table 103. Severe Exacerbation Outcomes

Trial	Outcome	Outcome Definition	Timepoint (Weeks)	Annualized Rate in Placebo Arm	Annualized Rate Ratio (95% CI)
VOYAGE[1] **ITT**	Severe exacerbations	Deterioration of asthma requiring any of the following: • Systemic corticosteroids for ≥3 days • Hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids	52	[redacted]	[redacted]
VOYAGE Omalizumab-eligible[1]	Severe exacerbations	Deterioration of asthma requiring any of the following: • Systemic corticosteroids for ≥3 days • Hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids	52	[redacted]	[redacted]
VOYAGE[1] **ITT**	Deterioration of asthma	Deterioration of asthma resulting in any of the following: • Systemic corticosteroids for ≥3 days • Increased ICS dose ≥4 times that at Visit 2	52	[redacted]	[redacted]
VOYAGE Omalizumab-eligible[1]	Deterioration of asthma	Deterioration of asthma resulting in any of the following: • Systemic corticosteroids for ≥3 days • Increased ICS dose ≥4 times that at Visit 2	52	[redacted]	[redacted]
IA05 [2 51]	Severe exacerbations	Worsening of asthma symptoms requiring any of the following: • Systemic corticosteroids for ≥3 days • Doubling of baseline ICS dose	24 52†	1.40 1.36	0.69 (0.53, 0.90) 0.57 (0.45, 0.72)†

† Data not included in ITC given that the study design included an ICS dose reduction phase after 24-weeks.

Abbreviations: BDP = beclomethasone dipropionate; CI = confidence interval; ICS = inhaled corticosteroid; NA = not applicable

Figure 20 Network Diagram



*Data from the ICATA trial will be included in a set of analyses for severe exacerbations only
Abbreviations: Q1M = once a month; Q2M = twice a month; Q2W = every two weeks

Exploratory Bucher ITCs based on the ITT (as randomized, all patients) and omalizumab-eligible populations from VOYAGE and IA05 were performed for the following outcomes of interest:

- Severe exacerbations (annualized rates)
- Deterioration of asthma from VOYAGE (post hoc analysis) vs. severe exacerbations from IA05 (annualized rates)
- Morning asthma symptom score at 24 weeks
- Change in PAQLQ(S)-IA at 24 weeks
- Discontinuations due to AEs at 52 weeks

The following section presents the key findings of the exploratory ITCs comparing dupilumab (100–200 mg Q2W) in the VOYAGE trial to omalizumab (75–375 mg Q1M or Q2M) in the IA05 trial. Results for dupilumab versus omalizumab are presented in Table 104. Note that given the differences observed across the included studies with regards to patient characteristics and definitions of severe exacerbations, findings of these analyses should be interpreted with caution.

12.4.1 ITT Population

The exploratory ITC results for the ITT population suggest that dupilumab has a numerical advantage over omalizumab in improving annualized rates of severe exacerbations (RR [95% CI]: 0.66 [0.42, 1.06]) and deterioration of asthma (RR [95% CI]: 0.66 [0.42, 1.03]) (Table 104). However, comparable effects on change from baseline in morning asthma score, rescue medication use (puffs per day), and PAQLQ(S)-IA were seen for both treatment groups at Week 24 (Table 104). The rates of discontinuations due to AEs were also similar for dupilumab and omalizumab following 52 weeks of treatment (Table 104).

For the sensitivity analyses of severe exacerbations (unadjusted, un-annualized) for the ITT population, dupilumab had a numerical advantage over omalizumab in improving severe exacerbations (RR [95% CI]: 0.67 [0.44, 1.04]). These results were based on the RE model, although no statistical heterogeneity was identified (i.e., the estimate of between-study variance was 0, I2 = 0%), hence the pooled estimate from the random-effect model was identical to the one from obtained from the fixed-effect analysis.

12.4.2 Omalizumab-eligible Population

The ITC results based on the omalizumab-eligible population were similar to the results based on the ITT population across all analyzed outcomes. The results suggest that dupilumab provides a numerical advantage over omalizumab in

improving annualized rates of severe exacerbations (RR [95% CI]: 0.60 [0.32, 1.13]) and deterioration of asthma (RR [95% CI]: 0.63 [0.34, 1.16]) (Table 104). No differences in change from baseline in morning asthma score, rescue medication use (puffs per day), and PAQLQ(S)-IA were seen for both treatment groups at Week 24 (Table 104). The rates of discontinuations due to AEs were also similar for dupilumab and omalizumab following 52 weeks of treatment for the omalizumab-eligible populations (Table 104).

Table 104 Bucher ITC Estimates and 95% Confidence Intervals for Dupilumab vs Omalizumab in Pediatric Patients (age 6 to <12 years) with Uncontrolled Moderate-to-Severe Asthma

Outcome	Included trials	ITT	Omalizumab-eligible
Severe Exacerbations (Annualized Rate Ratio)	VOYAGE, IA05		
	VOYAGE IA05, ICATA		
Asthma Deterioration (Annualized Rate Ratio)	VOYAGE, IA05		
Morning Asthma Symptom Score* (Mean Difference in CFB at 24-weeks)	VOYAGE, IA05		
Rescue Medication Puffs Per Day (Mean Difference in CFB at 24-weeks)	VOYAGE, IA05		
PAQLQ(S)-IA (Mean Difference in CFB at 24-weeks)	VOYAGE, IA05		
Discontinuations Due to AEs (OR End of Study)	VOYAGE, IA05		

Abbreviations: CFB = change from baseline; AEs = adverse events; PAQLQ(S)-IA = Pediatric Asthma Quality of Life Questionnaire with Standardized Activities–Interviewer Administered; OR = odds ratio

*Defined based on the outcome definition in VOYAGE, which evaluated participant's overall asthma symptoms experienced during the previous night.

Legend: Numerically favorable (p-value >0.05 and ≤ 0.15) Numerically comparable (p>0.15)

Appendix G – Extrapolation

N/A, no extrapolations.

Appendix H – Literature search for HRQoL data

N/A, no literature search for HRQoL data

Appendix I Mapping of HRQoL data

Utility Analysis

Utility data were collected at baseline, week 24 and week 52 in the VOYAGE trial. EQ-5D-Y score were collected for all patients, however as the instrument is only applicable to children above 8 years old two analyses will be performed:

- Including all patients in the ITT population
- Including only patients 8 years of age or older

This duplicated analysis will be only conducted for the overall trial population in the first instance. Should the utility estimates prove to be similar in the two analyses, further utility analyses for subgroups of patients from VOYAGE will only be conducted on patients of all ages (i.e., NOT restricted to patients 8 years or older). For subgroups that eventually become part of submissions to regulatory authorities, the duplicated analysis may be conducted in order to support the assumption made in the model and to provide as part of the evidence package.

Utility analyses will be performed using on-treatment records, both for the dupilumab and placebo populations.

Analyses of the EQ-5D-Y UK-weighted utility using the UK EQ-5D-3L value set and utility index as a function of treatment, control, and severe or moderate exacerbation and response will be conducted to derive utility values for the health states to be used in the four- and five-sub-state economic model.

Analyses specific to the Danish market will be conducted following the feedback from Danish authorities. Given the concerns regarding the derivation of EQ-5D-5L data from the EQ-5D-Y, Evidera recommended consulting the DMC regarding the acceptability of using the EQ-5D-3L for children and therefore of deviating from the DMC general guidance which favours the EQ-5D-5L. The EQ-5D-Y data from VOYAGE should then be analysed again, using the Danish value set for the EQ-5D-3L, for the purpose of the Danish submission.

Briefly, there is currently no endorsed value set of the EQ-5D-Y to support its use in economic evaluations and the EuroQol group advised against the use of the EQ-5D-3L value sets as a proxy value set for the EQ-5D-Y. In absence of a better option to derive EQ-5D-Y scores in children, the EQ-5D-3L value sets (with Danish tariffs) were used in the base case.

Appendix J Probabilistic sensitivity analyses

	Expected value	Standard error/N*	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)
Proportion of females at model start for Child cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age at model start (in years) for Child cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight (in kg) for Child cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IgE level (in IU/mL) for Child cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with weight <30 kg for Child cohort - 0-1 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with weight <30 kg for Child cohort - 2-3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with weight <30 kg for Child cohort - 4-5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with weight <30 kg for Child cohort - 6-7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with weight <30 kg for Child cohort - 8-9 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with weight <30 kg for Child cohort - 10-11 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with weight <30 kg for Child cohort - 12-13 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with weight <30 kg for Child cohort - 14-15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with weight <30 kg for Child cohort - 16-17 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with weight <30 kg for Child cohort - 18-19 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with weight <30 kg for Child cohort - 20-100 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients using Medium-dose ICS in Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients using High-dose ICS in Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients using Medium-dose ICS/LABA (combination inhaler) in Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients using High-dose ICS/LABA (combination inhaler) in Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients using LABA in Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Proportion of patients using LTRA in Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients using LAMA in Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients using Theophylline in Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients using SABA in Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of responders in Child cohort - Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of responders in Child cohort - Omalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of responders in Child cohort - Mepolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation rate per person-year for Child cohort: while using data from trials conducted in children - Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation rate per person-year for Child cohort: while using data from trials conducted in children - Omalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation rate per person-year for Child cohort: while using data from trials conducted in children - Mepolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation rate per person-year for Child cohort: while using data from trials conducted in adults/adolescents - Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation rate per person-year for Child cohort: while using data from trials conducted in adults/adolescents - Omalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation rate per person-year for Child cohort: while using data from trials conducted in adults/adolescents - Mepolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Background therapy alone - Controlled to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Background therapy alone - Uncontrolled to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Background therapy alone - Moderate Exacerbation to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Background therapy alone - Severe Exacerbation to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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TP for Child cohort: while using data from trials conducted in children - Period 1 - Background therapy alone - Controlled to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Background therapy alone - Uncontrolled to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Background therapy alone - Moderate Exacerbation to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Background therapy alone - Severe Exacerbation to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Background therapy alone - Controlled to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Background therapy alone - Uncontrolled to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Background therapy alone - Moderate Exacerbation to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Background therapy alone - Severe Exacerbation to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Background therapy alone - Controlled to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Background therapy alone - Uncontrolled to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Background therapy alone - Moderate Exacerbation to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Background therapy alone - Severe Exacerbation to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Background therapy alone - Controlled to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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TP for Child cohort: while using data from trials conducted in children - Period 2 - Background therapy alone - Severe Exacerbation to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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TP for Child cohort: while using data from trials conducted in children - Period 1 - Dupilumab + background therapy - All patients - Controlled to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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TP for Child cohort: while using data from trials conducted in children - Period 1 - Dupilumab + background therapy - All patients - Moderate Exacerbation to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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TP for Child cohort: while using data from trials conducted in children - Period 1 - Dupilumab + background therapy - All patients - Uncontrolled to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Dupilumab + background therapy - All patients - Moderate Exacerbation to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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TP for Child cohort: while using data from trials conducted in children - Period 1 - Dupilumab + background therapy - All patients - Moderate Exacerbation to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - All patients - Controlled to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - All patients - Severe Exacerbation to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - All patients - Moderate Exacerbation to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - All patients - Severe Exacerbation to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - All patients - Controlled to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - All patients - Uncontrolled to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - All patients - Moderate Exacerbation to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - All patients - Severe Exacerbation to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - All patients - Moderate Exacerbation to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - All patients - Severe Exacerbation to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - All patients - Severe Exacerbation to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - All patients - Controlled to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - All patients - Uncontrolled to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - All patients - Moderate Exacerbation to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - All patients - Severe Exacerbation to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - All patients - Controlled to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - All patients - Uncontrolled to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - All patients - Moderate Exacerbation to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - All patients - Severe Exacerbation to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Controlled to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Uncontrolled to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Moderate Exacerbation to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Severe Exacerbation to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Controlled to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Uncontrolled to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Moderate Exacerbation to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Severe Exacerbation to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Controlled to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Uncontrolled to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Moderate Exacerbation to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Severe Exacerbation to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Controlled to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Uncontrolled to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Moderate Exacerbation to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Severe Exacerbation to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Controlled to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Uncontrolled to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Moderate Exacerbation to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Severe Exacerbation to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Controlled to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Uncontrolled to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Moderate Exacerbation to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Severe Exacerbation to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Controlled to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Uncontrolled to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Moderate Exacerbation to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Severe Exacerbation to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Controlled to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Uncontrolled to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Moderate Exacerbation to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Severe Exacerbation to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of severe exacerbations treated with Office visit in Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of severe exacerbations treated with ED visit in Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of severe exacerbations treated with Hospitalisation in Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiplier applied to Severe Exacerbations, to adjust for population: Child cohort: while using data from trials conducted in children - Background therapy alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Multiplier applied to Severe Exacerbations, to adjust for population: Child cohort: while using data from trials conducted in children - Dupilumab + background therapy - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiplier applied to Severe Exacerbations, to adjust for population: Child cohort: while using data from trials conducted in children - Dupilumab + background therapy - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiplier applied to Severe Exacerbations, to adjust for population: Child cohort: while using data from trials conducted in adults/adolescents - Background therapy alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiplier applied to Severe Exacerbations, to adjust for population: Child cohort: while using data from trials conducted in adults/adolescents - Dupilumab + background therapy - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiplier applied to Severe Exacerbations, to adjust for population: Child cohort: while using data from trials conducted in adults/adolescents - Dupilumab + background therapy - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiplier applied to Moderate Exacerbations, to adjust for population: Child cohort: while using data from trials conducted in children - Background therapy alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiplier applied to Moderate Exacerbations, to adjust for population: Child cohort: while using data from trials conducted in children - Dupilumab + background therapy - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiplier applied to Moderate Exacerbations, to adjust for population: Child cohort: while using data from trials conducted in children - Dupilumab + background therapy - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiplier applied to proportion response, to adjust for population: Child cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of moderate exacerbations - Background therapy alone vs. Dupilumab - Child cohort: while using data from trials conducted in children - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of moderate exacerbations - Omalizumab vs. Dupilumab - Child cohort: while using data from trials conducted in children - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of moderate exacerbations - Mepolizumab vs. Dupilumab - Child cohort: while using data from trials conducted in children - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of severe exacerbations - Background therapy alone vs. Dupilumab - Child cohort: while using data from trials conducted in children - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of severe exacerbations - Omalizumab vs. Dupilumab - Child cohort: while using data from trials conducted in children - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of severe exacerbations - Mepolizumab vs. Dupilumab - Child cohort: while using data from trials conducted in children - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Relative Rate of moderate exacerbations - Omalizumab vs. Dupilumab - Child cohort: while using data from trials conducted in children - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of moderate exacerbations - Mepolizumab vs. Dupilumab - Child cohort: while using data from trials conducted in children - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of severe exacerbations - Omalizumab vs. Dupilumab - Child cohort: while using data from trials conducted in children - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of severe exacerbations - Mepolizumab vs. Dupilumab - Child cohort: while using data from trials conducted in children - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of moving to the 'Uncontrolled asthma' health state - Background therapy alone vs. Dupilumab - Child cohort: while using data from trials conducted in children - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of moving to the 'Uncontrolled asthma' health state - Omalizumab vs. Dupilumab - Child cohort: while using data from trials conducted in children - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of moving to the 'Uncontrolled asthma' health state - Mepolizumab vs. Dupilumab - Child cohort: while using data from trials conducted in children - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of moving to the 'Uncontrolled asthma' health state - Omalizumab vs. Dupilumab - Child cohort: while using data from trials conducted in children - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of moving to the 'Uncontrolled asthma' health state - Mepolizumab vs. Dupilumab - Child cohort: while using data from trials conducted in children - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative effect of experiencing Severe Exacerbation beyond the trial period (for child trials) for add-on therapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative effect of experiencing Severe Exacerbation beyond the trial period (for child trials) for Background therapy alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with ppFEV1 ≥80% among all patients treated with Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with ppFEV1 ≥80% among all patients treated with Background therapy alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with ppFEV1 ≥80% among all patients treated with Omalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with ppFEV1 ≥80% among all patients treated with Mepolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with ppFEV1 50%-79% among all patients treated with Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with ppFEV1 50%-79% among all patients treated with Background therapy alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with ppFEV1 50%-79% among all patients treated with Omalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with ppFEV1 50%-79% among all patients treated with Mepolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Proportion of patients with ppFEV1 <50% among all patients treated with Dupilumab	
Proportion of patients with ppFEV1 <50% among all patients treated with Background therapy alone	
Proportion of patients with ppFEV1 <50% among all patients treated with Omalizumab	
Proportion of patients with ppFEV1 <50% among all patients treated with Mepolizumab	
Proportion of patients with ppFEV1 ≥80% among responders treated with Dupilumab	
Proportion of patients with ppFEV1 ≥80% among responders treated with Omalizumab	
Proportion of patients with ppFEV1 ≥80% among responders treated with Mepolizumab	
Proportion of patients with ppFEV1 50%-79% among responders treated with Dupilumab	
Proportion of patients with ppFEV1 50%-79% among responders treated with Omalizumab	
Proportion of patients with ppFEV1 50%-79% among responders treated with Mepolizumab	
Proportion of patients with ppFEV1 <50% among responders treated with Dupilumab	
Proportion of patients with ppFEV1 <50% among responders treated with Omalizumab	
Proportion of patients with ppFEV1 <50% among responders treated with Mepolizumab	
Proportion of severe exacerbations requiring Office visit that are fatal - 6-11 years	
Proportion of severe exacerbations requiring Office visit that are fatal - 12-17 years	
Proportion of severe exacerbations requiring Office visit that are fatal - 18-24 years	
Proportion of severe exacerbations requiring Office visit that are fatal - 25-34 years	
Proportion of severe exacerbations requiring Office visit that are fatal - 35-44 years	
Proportion of severe exacerbations requiring Office visit that are fatal - 45-54 years	
Proportion of severe exacerbations requiring Office visit that are fatal - 55-64 years	
Proportion of severe exacerbations requiring Office visit that are fatal - 65-74 years	
Proportion of severe exacerbations requiring Office visit that are fatal - 75-100 years	
Proportion of severe exacerbations requiring ED visit that are fatal - 6-11 years	
Proportion of severe exacerbations requiring ED visit that are fatal - 12-17 years	
Proportion of severe exacerbations requiring ED visit that are fatal - 18-24 years	
Proportion of severe exacerbations requiring ED visit that are fatal - 25-34 years	
Proportion of severe exacerbations requiring ED visit that are fatal - 35-44 years	
Proportion of severe exacerbations requiring ED visit that are fatal - 45-54 years	
Proportion of severe exacerbations requiring ED visit that are fatal - 55-64 years	
Proportion of severe exacerbations requiring ED visit that are fatal - 65-74 years	

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Proportion of severe exacerbations requiring ED visit that are fatal - 75-100 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of severe exacerbations requiring Hospitalisation that are fatal - 6-11 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of severe exacerbations requiring Hospitalisation that are fatal - 12-17 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of severe exacerbations requiring Hospitalisation that are fatal - 18-24 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of severe exacerbations requiring Hospitalisation that are fatal - 25-34 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of severe exacerbations requiring Hospitalisation that are fatal - 35-44 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of severe exacerbations requiring Hospitalisation that are fatal - 45-54 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of severe exacerbations requiring Hospitalisation that are fatal - 55-64 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of severe exacerbations requiring Hospitalisation that are fatal - 65-74 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of severe exacerbations requiring Hospitalisation that are fatal - 75-100 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hazard ratio for other-cause mortality for patients with ppFEV1 50%-79% (versus patients with ppFEV1 ≥80%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hazard ratio for other-cause mortality for patients with ppFEV1 <50% (versus patients with ppFEV1 ≥80%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility in 'No Exacerbation' health state for Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility in 'Controlled Asthma' health state for Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility in 'Uncontrolled Asthma' health state for Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment utility adjustment - Dupilumab + background therapy - Child cohort: while using data from trials conducted in children - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment utility adjustment - Omalizumab + background therapy - Child cohort: while using data from trials conducted in children - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment utility adjustment - Mepolizumab + background therapy - Child cohort: while using data from trials conducted in children - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment utility adjustment - Dupilumab + background therapy - Child cohort: while using data from trials conducted in children - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment utility adjustment - Omalizumab + background therapy - Child cohort: while using data from trials conducted in children - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment utility adjustment - Mepolizumab + background therapy - Child cohort: while using data from trials conducted in children - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Moderate exacerbation-related utility - Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe exacerbation-related utility - exacerbation requiring Office visit - Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe exacerbation-related utility - exacerbation requiring ED visit - Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe exacerbation-related utility - exacerbation requiring Hospitalisation - Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate exacerbation-related utility: duration (in days) for add-on therapies - Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe exacerbation-related utility: duration (in days) for add-on therapies - exacerbation requiring Office visit - Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe exacerbation-related utility: duration (in days) for add-on therapies - exacerbation requiring ED visit - Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe exacerbation-related utility: duration (in days) for add-on therapies - exacerbation requiring Hospitalisation - Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate exacerbation-related utility: duration (in days) for background therapy - Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe exacerbation-related utility: duration (in days) for background therapy - exacerbation requiring Office visit - Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe exacerbation-related utility: duration (in days) for background therapy - exacerbation requiring ED visit - Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe exacerbation-related utility: duration (in days) for background therapy - exacerbation requiring Hospitalisation - Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caregivers' QoL-related utility adjustment - Dupilumab + background therapy - When the patient is a child (aged 6-<12) - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caregivers' QoL-related utility adjustment - Omalizumab + background therapy - When the patient is a child (aged 6-<12) - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caregivers' QoL-related utility adjustment - Mepolizumab + background therapy - When the patient is a child (aged 6-<12) - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caregivers' QoL-related utility adjustment - Dupilumab + background therapy - When the patient is a child (aged 6-<12) - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Caregivers' QoL-related utility adjustment - Omalizumab + background therapy - When the patient is a child (aged 6-<12) - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caregivers' QoL-related utility adjustment - Mepolizumab + background therapy - When the patient is a child (aged 6-<12) - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for healthcare worker's time for Subcutaneous administration: Office visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for healthcare worker's time for Subcutaneous administration: Home visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for healthcare worker's time for Subcutaneous administration: Hospital outpatient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for healthcare worker's time for Intravenous administration: Office visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for healthcare worker's time for Intravenous administration: Home visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for healthcare worker's time for Intravenous administration: Hospital outpatient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
One-off training cost for Subcutaneous self-administration (unit cost)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for Intravenous administration: Hospital day case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost per hour for room costs for Subcutaneous administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost per hour for room costs for Intravenous administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost per hour for equipment costs for Subcutaneous administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost per hour for equipment costs for Intravenous administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for utensil costs for Subcutaneous administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for utensil costs for Intravenous administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of administrations for Dupilumab administered in Office visit setting - External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of administrations for Omalizumab administered in Office visit setting - External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of administrations for Mepolizumab administered in Office visit setting - External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of administrations for Dupilumab administered in Home visit setting - External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of administrations for Omalizumab administered in Home visit setting - External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of administrations for Mepolizumab administered in Home visit setting - External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of administrations for Dupilumab administered in Hospital outpatient setting - External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Proportion of administrations for Omalizumab administered in Hospital outpatient setting - External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of administrations for Mepolizumab administered in Hospital outpatient setting - External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of administrations for Dupilumab that are self-administered - External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of administrations for Omalizumab that are self-administered - External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of administrations for Mepolizumab that are self-administered - External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost per monitoring hour for healthcare worker's time	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for transport for treatment administration: Office visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for transport for treatment administration: Home visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for transport for treatment administration: Hospital outpatient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for transport for treatment administration: Self-administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for hourly wage of patient and/or caregiver	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Outpatient visits: Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Outpatient visits: Pulmonologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Spirometry and FeNo tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Placeholder 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Placeholder 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Placeholder 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Placeholder 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'No Exacerbation' health state - External source of data in Children - Outpatient visits: Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'No Exacerbation' health state - External source of data in Children - Outpatient visits: Pulmonologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'No Exacerbation' health state - External source of data in Children - Spirometry and FeNo tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'No Exacerbation' health state - External source of data in Children - Placeholder 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Resource use per cycle in the 'No Exacerbation' health state - External source of data in Children - Placeholder 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'No Exacerbation' health state - External source of data in Children - Placeholder 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'No Exacerbation' health state - External source of data in Children - Placeholder 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'Controlled Asthma' health state - External source of data in Children - Outpatient visits: Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'Controlled Asthma' health state - External source of data in Children - Outpatient visits: Pulmonologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'Controlled Asthma' health state - External source of data in Children - Spirometry and FeNo tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'Controlled Asthma' health state - External source of data in Children - Placeholder 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'Controlled Asthma' health state - External source of data in Children - Placeholder 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'Controlled Asthma' health state - External source of data in Children - Placeholder 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'Controlled Asthma' health state - External source of data in Children - Placeholder 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'Uncontrolled Asthma' health state - External source of data in Children - Outpatient visits: Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'Uncontrolled Asthma' health state - External source of data in Children - Outpatient visits: Pulmonologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'Uncontrolled Asthma' health state - External source of data in Children - Spirometry and FeNo tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'Uncontrolled Asthma' health state - External source of data in Children - Placeholder 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'Uncontrolled Asthma' health state - External source of data in Children - Placeholder 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'Uncontrolled Asthma' health state - External source of data in Children - Placeholder 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Resource use per cycle in the 'Uncontrolled Asthma' health state - External source of data in Children - Placeholder 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Outpatient visits: Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Outpatient visits: Pulmonologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Outpatient visits: Psychiatrist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Spirometry and FeNO tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - OCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Emergency room attendance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Ambulance use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Hospitalisation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for moderate exacerbations - External source of data in Children - Outpatient visits: Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for moderate exacerbations - External source of data in Children - Outpatient visits: Pulmonologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for moderate exacerbations - External source of data in Children - Outpatient visits: Psychiatrist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for moderate exacerbations - External source of data in Children - Spirometry and FeNO tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for moderate exacerbations - External source of data in Children - OCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring Office visit - External source of data in Children - Outpatient visits: Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring Office visit - External source of data in Children - Outpatient visits: Pulmonologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring Office visit - External source of data in Children - Outpatient visits: Psychiatrist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring Office visit - External source of data in Children - Spirometry and FeNO tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring Office visit - External source of data in Children - OCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring ED visit - External source of data in Children - Outpatient visits: Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Resource use per cycle for severe exacerbations requiring ED visit - External source of data in Children - Outpatient visits: Pulmonologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring ED visit - External source of data in Children - Outpatient visits: Psychiatrist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring ED visit - External source of data in Children - Spirometry and FeNO tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring ED visit - External source of data in Children - OCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring ED visit - External source of data in Children - Emergency room attendance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring ED visit - External source of data in Children - Ambulance use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring Hospitalisation - External source of data in Children - Outpatient visits: Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring Hospitalisation - External source of data in Children - Outpatient visits: Pulmonologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring Hospitalisation - External source of data in Children - Outpatient visits: Psychiatrist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring Hospitalisation - External source of data in Children - Spirometry and FeNO tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring Hospitalisation - External source of data in Children - OCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring Hospitalisation - External source of data in Children - Emergency room attendance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring Hospitalisation - External source of data in Children - Ambulance use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring Hospitalisation - External source of data in Children - Hospitalisation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost per cycle of atopic comorbidities for monoclonal antibodies for the Child cohort - whilst using External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost per cycle of atopic comorbidities for Background therapy alone for the Child cohort - whilst using External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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N is used to calculate alpha & beta for all parameters that use a beta distribution. N should not be interpreted as a standard error

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Appendix K Omalizumab dosing scheme

Figure 21 Omalizumab Doses (mg per dose) Administered Every Four Weeks by Body Weight and Baseline IgE, Europe

	Body weight (kg)									
Baseline IgE (IU/ml)	≥20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
≥30-100	75	75	75	150	150	150	150	150	300	300
>100-200	150	150	150	300	300	300	300	300	450	600
>200-300	150	150	225	300	300	450	450	450	600	
>300-400	225	225	300	450	450	450	600	600		
>400-500	225	300	450	450	600	600				
>500-600	300	300	450	600	600					
>600-700	300		450	600						
>700-800										
>800-900	ADMINISTRATION EVERY 2 WEEKS SEE TABLE 3									
>900-1000										
>1000-1100										

Appendix L Adult and adolescent population for economic assessment

Main characteristics of included studies

The main characteristics of the studies included in the economic assessment for patients aged ≥12 are presented below. An overview of the main study characteristics is provided in Table 105 and baseline characteristics for each study are summarised in Table 106. As agreed with the Medicines Council, the tables provided resemble the study and baseline characteristics tables in the Medicines Council's background for the treatment guideline for biological treatment of severe asthma for adults and adolescents 12 years and older (104).

QUEST (Castro et al 2018)

QUEST was a randomised, double-blind, placebo-controlled, parallel-group, phase 3 study that assessed the efficacy and safety of dupilumab in patients with uncontrolled moderate-to-severe asthma (105-107).

A total of 1902 patients aged ≥12 years were randomised (2:2:1:1) by use of a centralised treatment allocation system to receive s.c. dupilumab 200 mg Q2W (loading dose 400 mg), 300 mg Q2W (loading dose 600 mg) or 2 matched-volume placebo groups for 52 weeks. Background asthma-controller medicines were continued at a stable dose throughout the trial. Use of LABA, long-acting muscarinic antagonists, antileukotriene agents and methylxanthines was permitted. Throughout the trial, patients were permitted to use a short-acting β2-adrenergic-receptor agonist as necessary for symptom relief.

The study included patients with physician-diagnosed persistent asthma for ≥12 months according to the GINA 2014 guidelines, current treatment with medium-to-high-dose ICS plus up to 2 additional controllers, FEV1 of ≤80% of the predicted normal (or ≤90% of the predicted normal in patients 12-17 years old), FEV1 reversibility of ≥12% and 200 mL; ACQ-5 score of ≥1.5 and a worsening of asthma in the previous year that led to hospitalisation, emergency medical care

or treatment with systemic glucocorticoids for ≥3 days. Patients were recruited irrespective of baseline blood EOS count or levels of biomarkers of type 2 inflammation, e.g. FeNO or IgE. Randomisation was stratified according to age (<18 years or ≥18 years), peripheral-blood EOS count (<300 or ≥300/µL) at screening, ICS dose (medium or high) and by country. Current smokers or former smokers with a smoking history of >10 pack years, and patients with COPD or other lung diseases were excluded.

The primary efficacy outcomes were the annualised rate of severe exacerbation events during the 52-week intervention period and the absolute change from baseline in the FEV1 before bronchodilator use at week 12 in the broad ITT population. A severe asthma exacerbation was defined as a deterioration of asthma leading to treatment for ≥3 days with systemic glucocorticoids or hospitalisation or an emergency department visit leading to treatment with systemic glucocorticoids. Secondary outcomes and pre-specified subgroup analyses included the annualised rate of severe exacerbation events and change from baseline in FEV1 at week 12 in patients with elevated FeNO (≥25ppb), blood EOS count ≥150 cells/µL and ≥300 cells/µL, change from baseline in ACQ-5 score and AQLQ score at week 24, and safety.

Efficacy analyses were performed in the broad ITT population, defined as all the patients who underwent randomisation.

VENTURE (Rabe et al 2018)

VENTURE was a randomised, double-blind, placebo-controlled, parallel-group, phase 3 study that assessed the efficacy and safety of dupilumab in patients with OCS-dependent severe asthma (108, 109).

After an OCS dose-adjustment period of 3-10 weeks, a total of 210 patients were randomised 1:1 by use of a centralized treatment allocation system to receive dupilumab 300 mg Q2W (loading dose 600 mg) or placebo. The 24-week intervention period consisted of a 4-week induction period, during which the adjusted OCS dose was continued; a 16-week period (weeks 4 to 20) during which the OCS dose was adjusted down every 4 weeks according to a protocol prespecified algorithm; and a 4-week maintenance period, during which patients continued the OCS dose that was established at week 20. The adjusted OCS dose was defined as the lowest dose that a patient could receive without having an increase of ≥0.5 (i.e., the minimal clinically relevant difference [MCID]) in the ACQ-5 score, a severe exacerbation or any clinically significant event leading to an upward adjustment in the OCS dose. Background asthma controllers were continued at a stable dose and the use of a short-acting β2-agonist was permitted as needed for asthma symptoms.

The study included patients ≥12 years who had had physician-diagnosed asthma for ≥1 year according to the GINA 2014 guidelines and who had been receiving treatment with regular systemic glucocorticoids in the previous 6 months (5 to 35 mg/ day of prednisone or prednisolone or equivalent). During the 4 weeks before screening, their treatment had to also include a high-dose ICS (fluticasone propionate at a total daily dose of >500 µg or equipotent equivalent) in combination with up to 2 controllers (i.e. a LABA or leukotriene-receptor antagonist) for ≥3 months; FEV1 before bronchodilator use of ≤80% of the predicted normal value (or ≤90% of the predicted normal value in adolescents), FEV1 reversibility of ≥12% and 200 mL, or airway hyperresponsiveness documented in the 12 months before screening. Patients were recruited with no minimum requirements regarding a baseline blood or sputum EOS count or any other type 2 biomarkers. Randomisation was stratified according to the adjusted OCS dose (≤10 mg/day *vs* >10 mg/day of prednisone or prednisolone) and by country. Current smokers or former smokers with a smoking history of >10 pack years, and patients with COPD or other lung diseases were excluded.

The primary efficacy outcome was the % reduction in the OCS dose from baseline to week 24 while asthma control was maintained. Between weeks 20 and 24 asthma control was considered to be maintained if no clinically significant event (based on investigator judgment) leading to an upward adjustment in the OCS dose occurred. For patients who had an exacerbation, the final OCS dose was considered to be 1 step higher than the dose they had been receiving at the time of the exacerbation. Key secondary efficacy endpoints that were assessed in patients with maintained asthma control were the proportion of patients with a reduction from baseline of ≥50% in the OCS dose and the proportion of patients who had a reduction in the OCS dose to ≤5 mg per day. Other endpoints included the proportion of patients who no longer used oral glucocorticoids, the annualised rate of severe exacerbation events (defined as events leading to

hospitalisation, an emergency department visit or treatment for ≥3 days with systemic glucocorticoids at ≥2 times the current dose of OCS) during the 24-week intervention period; the absolute change from baseline in the FEV1 before bronchodilator use at weeks 2, 4, 8, 12, 16, 20, and 24; and the change from baseline in ACQ-5 score and AQLQ score at week 24, and safety. Prespecified subgroup analyses included patients with elevated FeNO (≥25ppb), blood EOS count ≥150 cells/µL and ≥300 cells/µL.

Efficacy analyses were performed in the broad ITT treat population, which included all randomised patients. The safety population included all the patients who received ≥1 dose or a partial dose of dupilumab or placebo, and data were analysed according to the treatment regimen received.

The study characteristics for QUEST and VENTURE are summarized in Table 105.

Table 105 Study characteristics for QUEST and VENTURE

Reference and NCT number	Study design	Follow-up	Age (years)	Relevant outcomes	Asthma diagnosis before or at randomisation documented by	Asthma severity	Refractory asthma (e.g. exacerbations, symptoms, FEV1)	Reduced lung function	EOS (cells/µL)	ICS dose	2nd controller	OCS	# patients randomised per group
Castro 2018 (main) (QUEST) 02414854 *Castro 2019 (lung function)* *Corren 2019b (allergic subgroups)*	Randomised, double-blind, placebo-controlled trial	52 weeks	≥12	Exacerbations FEV1 ACQ-5 AQLQ Symptom score EQ-5D-5L SAE Discontinuations	Airway reversibility (FEV1 ≥12% and 200 mL) *Allergic asthma was defined as total serum IgE ≥30 IU/mL and ≥1 positive perennial aeroallergen-specific IgE value (≥0.35 kU/L) at baseline*[a]	Moderate-to-severe	Asthma worsening in the previous year leading to hospitalisation, emergency medical care or treatment with systemic CS for ≥3 days	FEV1 ≤80% for adults; ≤90% for adolescents	Not inclusion criterion. Randomisation stratified by EOS at screening (≥300 cells/µL, <300 cells/µL)	Medium-to-high (≥500 µg FT or equivalent)	Additional controller drugs required	Not specified	1902 (randomised 2:1, DUP *vs* PBO): DUP 200 mg (N=631), PBO (N=317), DUP 300 mg (N=633), PBO (N=321) all s.c. and Q2W
Rabe 2018 (main) (VENTURE) 02528214 *Rabe 2019 (lung function)*	Randomised, double-blind, placebo-controlled trial	24 weeks	≥12	Exacerbations OCS reduction FEV1 ACQ-5 AQLQ SAE Discontinuations	Airway reversibility (FEV1 ≥12% and 200 mL) or airway hyperresponsiveness (methacholine: PC20 of ≤8 mg/mL)	Severe	Not specified	FEV1 ≤80% for adults; ≤90% for adolescents	Not inclusion or stratification criteria. Subgroup analysis (≥300 cells/µL or <300 cells/µL; ≥150 cells/µL or <150 cells/µL)	High (>500 µg FT or equivalent)	Additional controller drugs required	All OCS dependent (5-35 mg/day prednisone / prednisolone or equivalent)	210: DUP 300 mg (N=103), PBO (N=107) all s.c. and Q2W

References in italics are secondary publications of the primary reference above.

[a] The following perennial allergens were included: *Dermatophagoides farinae, Dermatophagoides pteronyssinus, Alternaria alternata, Cladosporium herbarum*, cat and dog danders, German cockroach, oriental cockroach and *Aspergillus fumigatus*

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CS, corticosteroids; DUP, dupilumab; EOS, blood eosinophils; EQ-5D-5L, European Quality of Life Working Group Health Status Measure

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5 Dimensions, 5 Levels; FEV1, forced expiratory volume in 1 s; FT, fluticasone propionate; ICS, inhaled corticosteroids; IgE, immunoglobulin E; LABA, long-acting beta agonist; OCS, oral corticosteroids; PBO, placebo; PC20, provocative concentration of inhaled methacholine needed to reduce FEV1 by 20%; QoL, quality of life; Q2W, every 2 weeks; Q2W, every 4 weeks; SAE, serious adverse event; s.c., subcutaneously

Table 106 Baseline characteristics for QUEST and VENTURE

Reference	n		Female (%)		Race White (%)		Mean age (years)		# exacerbations in last year		FEV1 (L)		FEV1 % predicted		Mean ACQ score		LABA use* (%)		High dose ICS use (%)		OCS use %, daily dose		FeNO (ppb)		EOS (cells/µL)		IgE (IU/mL)	
	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO
Castro 2018 (main) (QUEST) ***Castro 2019 (lung function)***	631	317	61	63	Not reported		47.9	48.2	2.1	2.1	1.78	1.76	58.4	58.4	2.8	2.7	LABA or other second controller required		50	54	Not reported		34.5	34.5	349	370	461	394
Corren 2019b (allergic subgroup)	360	183	54	55	Not reported		45.5	44.0	2.0	1.9	1.85	1.84	Not reported		2.7	2.7	LABA or other second controller required		Not reported; medium-to-high-dose inclusion criterion		Not reported		25	27	240	290	304	337
Rabe 2018 (main) (VENTURE) ***Rabe 2019 (lung function)***	103	107	60	61	94	93	51.9	50.7	2.0	2.2	1.53	1.63	51.6	52.7	2.4	2.6	LABA or other second controller required		Inclusion criterion		Inclusion criterion; Dose 10.00 (5.0 to 35.0)[b]		35.6	39.6	370	325	Not reported	

Data are presented for 200 mg dupilumab Q2W *vs* placebo, except for the VENTURE study (300 mg dupilumab Q2W *vs* placebo). References in italics are secondary publications of the primary reference above. Severe asthma was an inclusion criterion for the VENTURE study (Rabe 2018); the proportion of subjects with severe asthma was not reported in the other studies

[a] or equivalent 2nd controller; [b] median (range) in both the dupilumab and placebo groups

ACQ, Asthma Control Questionnaire; DUP, dupilumab; EOS, blood eosinophils; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; IgE; immunoglobulin E; IU, international unit; LABA, long-acting beta agonist; n, number of subjects in the treatment group; OCS, oral corticosteroids; PBO, placebo; ppb, parts per billion; Q2W, every 2 weeks.

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Subgroup populations

Studies in non-OCS dependent asthma and OCS-dependent asthma

The Medicines Council's protocol (110) states that data for the outcomes related to maintenance OCS treatment should be presented for the 300 mg dupilumab dose, while data on all other outcomes should be presented for the 200 mg dose. The 300 mg dose is indicated for patients >12 years with severe asthma treated with OCS, and for patients >12 years with severe asthma and co-morbid atopic dermatitis for which dupilumab is also approved in the EU, including Denmark.

Since patients treated with maintenance OCS can be considered a separate population, it was agreed with the Medicines Council to present the results for the 300 mg dose for all outcomes. This is also deemed relevant since approximately 50% of the Danish patients <18 years could be candidates for treatment with 300 mg dupilumab due to concomitant atopic dermatitis and approximately 10-20% of the Danish adult patients could be candidates for treatment with the 300 mg dose due to maintenance treatment with OCS (110).

Thus, for 2 of the clinical questions (increased EOS population *vs* mepolizumab and increased FeNO population *vs* placebo), where data are available, we present data both for the 200 mg dupilumab dose in a patient population with moderate-to-severe uncontrolled, persistent asthma, and for the 300 mg dupilumab dose in a patient population with severe asthma treated with maintenance OCS.

Dupilumab subgroups covering the protocol-defined populations

The 3 pivotal dupilumab studies had broad eligibility criteria, and patients were not selected for enrolment based on phenotypic traits. Different subgroup analyses of the 3 studies have been performed based on EOS and FeNO levels, which largely cover the 3 patient populations defined in the protocol provided by the Medicines Council. Thus, where available, we used data for the following dupilumab subgroups in this application:

- Increased EOS subgroup to assess the added clinical value of dupilumab *vs* mepolizumab. This subgroup includes patients with baseline blood EOS ≥150 cells/µL.
- Allergic subgroup to assess the added clinical value of dupilumab *vs* omalizumab. This subgroup includes patients with allergy, defined as total serum IgE ≥30 IU/mL and ≥1 positive perennial aeroallergen-specific IgE value (≥0.35 kU/L), and concomitant baseline blood EOS ≥150 cells/µL, or allergy and concomitant FeNO ≥25 ppb at baseline.
- Increased FeNO subgroup to assess the added clinical value of dupilumab *vs* placebo. The protocol provided by the Medicines Council defines this subpopulation as patients with increased FeNO *without* concomitant eosinophilia and *without* concomitant allergy. However, data for this subgroup are not reported. Therefore, available data for patients with elevated baseline FeNO (≥25 ppb) regardless of EOS and allergy status is provided.

Asthma is a heterogeneous disease and most patients are characterised by having more than 1 of several phenotypic traits. Hence, patients with eosinophilic asthma are often also allergic and *vice versa*. This has been confirmed in a recent real-world practice study, including patients from Europe (53). Similarly, patients with elevated FeNO will often possess phenotypic traits of eosinophilic and/or allergic asthma as well. This has also recently been confirmed in another real-world study, including patients from Sweden (52). Only 49 patients in the QUEST study matched the "FeNO only" patient population defined in the protocol, which only includes the patients who are not included in any of the other 2 populations. As data from these 49 patients are not available, and since there is also a significant overlap between the eosinophilic and allergic patient populations defined by current Danish treatment guidelines, we have provided available data for patients with elevated baseline FeNO (≥25 ppb) regardless of EOS and allergy status (Figure 23).

Figure 22 Patient populations in severe asthma

Figure 23: Patient populations in serve asthma

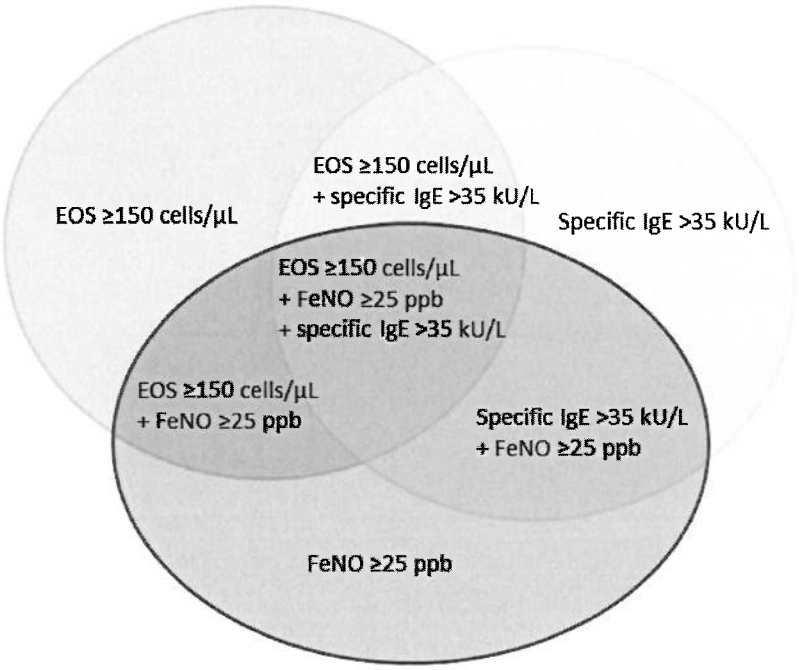


Table 108 provides a summary of the main study characteristics of the 3 dupilumab studies, while Table 110 summarises the subgroups where relevant published data are available. For each of the clinical questions, some outcomes were not available in the specific dupilumab subgroup. In those cases, we provide data for the best alternative population, for example data for the entire allergic population regardless of EOS and FeNO status or, in some cases, data for the ITT population.

Table 107 Overall summary of the dupilumab studies

Table 108: Overall summary of the Dupilumab studies

Dupilumab population	Study	N	Dupilumab dose(s)	Study population	Asthma severity	ICS dose	2nd controller required?	OCS	Age
ITT	QUEST (Castro 2018)	1902 [a]	200 mg Q2W 300 mg Q2W	Uncontrolled, persistent asthma	Moderate-severe	Medium-high	Yes, LABA or other	Not specified	≥12
	VENTURE (Rabe 2018)	210	300 mg Q2W	OCS-dependent asthma	Severe	High	Yes, LABA or other	5-35 mg/day prednisone or equivalent	≥12

[a] includes all doses and dosing frequencies. Only data for the relevant dose and frequency (200 mg Q2W) are used in this application

ICS, inhaled corticosteroids; ITT, intention-to-treat; LABA, long-acting beta agonist; N, number of subjects randomised; OCS, oral corticosteroids; Q2W, every 2 weeks; Q2W, every 4 weeks

Table 109 **Relevant subgroups from the dupilumab studies with available published data**

Table 110 Relevant subgroups from the dupilumab studies with available published data

Dupilumab subgroup	Study	N (% of ITT)	Dupilumab dose relevant for application	EOS level at baseline (cells/µL)	FeNO level at baseline (ppb)	IgE/ allergens
Asthma with type 2-inflammation characterised by eosinophilia						
Increased EOS subgroups	QUEST	669 (35%)	200 mg Q2W	≥150	Any level	Any level
	VEN-TURE	150 (71%)	300 mg Q2W	≥150	Any level	Any level
Asthma characterised by allergy and concomitant eosinophilia or characterised by allergy and concomitant increased FeNO						
Allergic sub-groups	QUEST	384 (20%)	200 mg Q2W	≥150	Any level	Total serum IgE ≥30 IU/mL and ≥1 positive perennial aeroallergen-specific IgE value (≥0.35 kU/L)[a]
		284 (15%)	200 mg Q2W	Any level	≥25	
		543 (29%)	200 mg Q2W	Any level	Any level	
Asthma characterised by increased FeNO						
Increased FeNO sub-groups	QUEST	461 (24%)	200 mg Q2W	Any level	≥25	Any level
	VEN-TURE	114 (54%)	300 mg Q2W	Any level	≥25	Any level

[a] includes the following perennial allergens: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Alternaria alternata*, *Cladosporium herbarum*, cat and dog danders, German cockroach, oriental cockroach and *Aspergillus fumigatus*. Percutaneous allergy skin testing was not performed, and symptoms on relevant exposure for the antigen were not recorded

EOS, blood eosinophils; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; ITT, intention-to-treat; ppb, parts per billion; Q2W, every 2 weeks

Resource use and costs adult/adultescents

Administration costs

The time of administration etc. was the same for adults/adolescent as for children. The DMC estimates that up to 70% of adult/adolescent patients self-administered their treatment, with the remaining 30% assumed to be administered by a healthcare professional in a hospital outpatient setting(62).

Table 111. Resource use associated with drug administration (Adult/Adolescent population)

Treatment	Duration (Minutes per Administration)	% Administered by Healthcare Professional			% self-Administered	
		Office Visit	Home Visit	Hospital Out-patient	%	N
Dupilumab (alone)	10 mins	0.0%	0.0%	30.0%	70.0%	100
Background therapy alone						
Omalizumab (alone)	10 mins	0.0%	0.0%	30.0%	70.0%	100
Mepolizumab (alone)	10 mins	0.0%	0.0%	30.0%	70.0%	100

Monitoring costs

For adults, a 15-minute monitoring period is assumed for the initial administration with no monitoring assumed for subsequent administrations.

Table 112. Monitoring Unit Cost as applied in the model

	Initial Administration Unit Cost	Subsequent Admin-istration Unit Cost	Source
Monitoring by nurse for Adults	DKK 554 per working hour; costed at 15 minutes per hour (= DKK 138.50 per hour)	N/A	Medicinrådet Værdisætning af enhedsomkostninger,vers 1.2

Routine visits and Disease management

Table 113. Routine Care Resource Use per Cycle (4 Weeks) by Level of Control

Resource	In the 'Controlled Asthma' Health State*		In the 'Uncontrolled Asthma' Health State	
	Mean	SE†	Mean	SE†
Adults/adolescents				
Outpatient visits: Nurse	0.333	0.067	0.500	0.100
Outpatient visits: Pulmonologist	0.333	0.067	0.500	0.100
Spirometry and FeNO tests	0.333	0.067	0.500	0.100

Source: For controlled asthma, a monitoring visit every 12 weeks is assumed (20 min nurse, 1 hours physician to do tests, spiro, reversibility, mannitol test, FeNO, blood samples (IgE, eosinophilic status, BAT) / For uncontrolled asthma, a monitoring visit every 8th week is assumed, (20 min nurse, 1 hours physician to do tests, spiro, reversibility, mannitol test, FeNO, blood samples (IgE, eosinophilic status, BAT)

Unit costs for disease management resource use in Denmark were collected from the DMC catalogue of unit costs (79) or other publicly available sources when necessary.

Table 114. Routine Care Unit Costs

Resource	Unit Cost	Source
	Adult/Adolescent population	
Outpatient visits: Nurse	DKK 185.97	Duration of visit: elicited from Danish KOLs via expert in out/validation (20 minutes)
Outpatient visits: Pulmonologist	DKK 1,186.00	www.krl.dk
Spirometry and FeNo tests	DKK 264.75	www.laeger.dk; Performed by a specialist

Appendix M. Relative efficacy of dupilumab versus Omalizumab and Mepolizumab Adult/Adolescent population

In relation to section 8.2.2.4: The adult/adolescent model allowed a comparison versus other biologics including response assessment utilizing numerous assumptions. Two sets of RRs for patients responding to the add-on biologics (1) were incorporated to estimate transition probabilities for patients who respond to other biologics:

- Relative effects as obtained from the ITC (among all patients) versus dupilumab were assumed to apply for responders, implying that although the risk of exacerbations may change in responders, the relative effects for biologics versus dupilumab remain constant regardless of response status.
- Relative effects for responders versus background therapy, as obtained from the reimbursement submissions of each biologic (see Appendix M), were expressed versus dupilumab (2). This approach is consistent with the approach previously adopted in the mepolizumab (64) submissions.

In the base case, the relative effects for responders versus background therapy as obtained from the reimbursement submissions were used. This option was considered most appropriate, given relative effects differ between responders to treatment and the overall patient population, as well as by definition of response. For example, when comparing versus mepolizumab, the definitions of response were inconsistent:

- Mepolizumab: Patients who do not experience a worsening in exacerbation rates are defined as responders
- Dupilumab: Patients who experience a 50% improvement or more in exacerbation rates are considered responders

By definition, even if mepolizumab and dupilumab were equivalent in terms of exacerbation rate reduction, due to the stricter definition adopted for dupilumab, a lower exacerbation rate would be observed among dupilumab responders compared to mepolizumab responders, thereby necessitating alternative relative effects for responders as compared to all patients. The relative effects based on the ITC are used in scenario analysis. However, since that implies an equivalent response definition rule between treatments, the response rate for mepolizumab was lowered in this scenario from 90.9% to 76.7% (Appendix R. Response Rates for Other Monoclonal Antibodies by Population).

Severe Exacerbations

The Table 115 summarises the relative efficacy in reducing severe exacerbations for omalizumab and mepolizumab patients versus dupilumab in the adult/adolescent population of patients outlined in Table 35 without steroid dependency. Data from the Bucher ITCs is used in the base case in the adult/adolescent population.

Table 115. Relative Rates of Experiencing Severe Exacerbations versus Dupilumab – Patients Not on Maintenance OCS

Treatment	Mean	95% Lower	95% Upper
(Adult/Adolescent Population) Bucher Itc[a]			
[redacted]	[redacted]	[redacted]	[redacted]

- [1] These RRs were used post-response assessment, when such an assessment was included in the analysis; they were not used otherwise.
- [2] Relative effects were expressed versus dupilumab for consistency with how relative effects were expressed among all patients and when data from the indirect comparisons were used. Relative effects were expressed versus dupilumab using $\ln RR_{AB} = \ln RR_{AC} - \ln RR_{BC}$ and $SE(\ln RR_{AB}) = \sqrt{[SE(\ln RR_{AC})^2 + SE(\ln RR_{BC})}$.[2]

[redacted]			

Source: a. ITC;(111)

Table 116Table 117 summarises the relative efficacy in reducing severe exacerbations for all biologic responders versus placebo, and the implied relative efficacy versus dupilumab in a population of adult/adolescent patients without steroid dependency.

Table 116. Relative Rates of Experiencing Severe Exacerbations versus Dupilumab – Responders Not on Maintenance OCS (Adult/Adolescent population)

	Dupilumab versus Placebo[a]		Biologic Comparator versus Placebo		Biologic Comparator versus Dupilumab[d]		
	Mean	SE	Mean	SE	Mean	Lower	Upper
[redacted]							
[redacted]							

Source:

a. Estimated based on the number of transitions in each respective population. Rate of exacerbations estimated as the number of transitions to severe exacerbation divided by patient-years, estimated as sum of transitions * years in cycle. Relative rate estimated as ratio of dupilumab rate and placebo rate. Standard error estimated as √(1/a+1/b) where a and b reflect the number of severe exacerbations observed in the placebo and dupilumab arms.

Norman et al. 2013; Page 241, ITT population, INNOVATE(61)

b. Appendix N. Calculations of Relative Risks for Responders to Other Monoclonal Antibodies (Adult/Adolescent Model))
c. Mepolizumab submission to NICE(112) (see Appendix N. Calculations of Relative Risks for Responders to Other Monoclonal Antibodies (Adult/Adolescent Model, based on ITT population in MENSA)
d. Relative effects were expressed versus dupilumab using $lnRR_{AB} = lnRR_{AC} - lnRR_{BC}$ and $SE(lnRR_{AB}) = \sqrt{[SE(lnRR_{AC})^2 + SE(lnRR_{BC})^2}$

For patients on mOCS, relative efficacy estimates from the indirect comparisons were only available versus mepolizumab as outlined in Table 117. Data for responders are provided in Table 118.

Table 117. Relative Rates of Experiencing Severe Exacerbations – All Patients on Maintenance OCS (Adult/Adolescent population)

Treatment	Mean	95% Lower	95% Upper
	Bucher ITC		
Mepolizumab + Background Therapy	[redacted]	[redacted]	[redacted]

Source: ITC;(111)

Table 118. Relative Rates of Experiencing Severe Exacerbations – Responders on Maintenance OCS – Mepolizumab Like population (Adult/Adolescent population)

	Dupilumab versus Placebo[a]		Biologic Comparator versus Placebo		Biologic Comparator versus Dupilumab[b]		
	Mean	**SE**	**Mean**	**SE**	**Mean**	**Lower**	**Upper**
Reduction in OCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reduction in OCS or Exacerbations	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]

Source:

a. Estimated based on the number of transitions in each respective population. Rate of exacerbations estimated as the number of transitions to severe exacerbation divided by patient-years, estimated as sum of transitions * years in cycle. Relative rate estimated as the ratio of dupilumab rate and placebo rate. Standard error estimated as $\sqrt{(1/a+1/b)}$, where a and b reflect the number of severe exacerbations observed in the placebo and dupilumab arms.

Mepolizumab submission to NICE(112)(see

Appendix N. Calculations of Relative Risks for Responders to Other Monoclonal Antibodies (Adult/Adolescent Model), based on ITT population restricted to OCS patients)

Moderate Exacerbations, Uncontrolled Asthma and Lung Function

In addition to the risk of experiencing severe exacerbations, the adult/adolescent model necessitated data on the transition probabilities to moderate exacerbations and uncontrolled asthma, but also the distribution in ppFEV1 in scenario analysis. Informing these inputs for biologic comparators was hampered by limited data and/or data available in an inconsistent format compared to what was required by the model.

Moderate Exacerbations

The risk of experiencing moderate exacerbations was not assessed in the indirect comparisons as this was not collected in mepolizumab trials, and in the case of omalizumab, alternative definitions were used. For example, in the INNOVATE trial, this was defined as a worsening of asthma symptoms requiring systemic CS but not fitting criteria for severe exacerbations,(61) whilst in the Liberty Asthma QUEST trial, this was defined based on a number of criteria Table 119.

Table 119. Comparison of Definitions of Moderate Exacerbations Across Trials

	LIBERTY ASTHMA QUEST(105)	INNOVATE(61)
PEF	A decrease in AM or PM PEF of 30% or more on 2 consecutive days of treatment, based on the defined stability limit	Worsening of asthma symptoms requiring treatment with systemic CS not meeting the definition of clinically severe (PEF/FEV_1 < 60% of personal best, requiring systemic CS] resulting in hospitalisation or ER treatment, in the past 12 months)
Rescue Medication	≥ 6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24-hour period (compared to baseline) on 2 consecutive days	
Nighttime Awakenings	NA	
Symptoms	NA	
Lung Function	≥ 20% decrease in pre-bronchodilator FEV_1 compared with baseline	
ICS Dose	Increase in ICS dose ≥ 4 times than the dose at Visit 2	

Due to the inconsistent definitions adopted, any analyses comparing moderate exacerbation risks between biologics would be subject to bias. Therefore, in the base case in the adult/adolescent model, it was assumed that the moderate exacerbation risk would be equivalent across biologic treatments. A RR of 1 was therefore implemented, which was varied by 20% in sensitivity analyses to determine the influence of this assumption.

Assuming relative efficacy would be unaffected by the inconsistent definitions, RRs of experiencing moderate exacerbations were derived, which were examined as an exploratory scenario in the adult/adolescent model Table 120.

Table 120. Relative Rates of Experiencing Moderate Exacerbations – Exploratory Analyses (Adults/Adolescents)

Comparator	Biologic vs Placebo	Dupilumab vs Placebo[b]	Biologic vs Dupilumab[c]
All Patients			
Omalizumab	[redacted]	[redacted]	[redacted]
Responders			
Omalizumab	[redacted]	[redacted]	[redacted]

Source:

a. Norman et al. 2013; Table 66, INNOVATE: all(61)

b. Estimated based on the number of transitions in each respective population. Rate of exacerbations estimated as the number of transitions to severe exacerbation divided by patient-years, estimated as the sum of transitions * years in cycle. Relative rate estimated as ratio of dupilumab rate and placebo rate. Standard error estimated as √(1/a+1/b), where a and b reflect the number of severe exacerbations observed in the placebo and dupilumab arms.

c. Relative effects were expressed versus dupilumab using $\ln RR_{AB} = \ln RR_{AC} - \ln RR_{BC}$ and $SE(\ln RR_{AB}) = \sqrt{[SE(\ln RR_{AC})^2 + SE(\ln RR_{BC})^2}$

Lung Function

Although mean change in FEV1 in litres was available from the indirect comparison, the distribution of patients across ppFEV1 categories was assumed to be equal across biologics in the adult/adolescent model. To transform the mean change in FEV1 in litres to ppFEV1, several assumptions would have been needed. As the indirect comparisons indicated that FEV1 results were favourable for dupilumab, this assumption was considered conservative.

OCS Reduction

Relative effects, expressed as odds ratios (ORs) in terms of OCS reduction, were only available versus mepolizumab. The following outcomes were available versus mepolizumab:

- Reduction in OCS dose < 5 mg/day (OR)
- Reduction in OCS dose = 50% (OR)

Reduction in the daily OCS dose to a dose < 5 mg/day was available for both treatments. Withdrawal from OCS (i.e., 100% reduction) was available versus mepolizumab. These ORs (Table 121) are used to estimate the proportion of adult/adolescent patients achieving a daily dose < 5 mg and those withdrawing from treatment with mepolizumab. In the absence of information to inform withdrawal among responders, it is assumed that the ORs of withdrawing from treatment were consistent among all adult/adolescent patients and responders.

Table 121. Odds Ratios – OCS Reduction (Adult/Adolescent population)

	Withdrawal from OCS			Reduction to a Daily Dose < 5mg		
Treatment	**Mean**	**95% Lower**	**95% Upper**	**Mean**	**95% Lower**	**95% Upper**
			ITC[a]			
Mepolizumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: a. ITC;(111)

Proportion of Patients Achieving Response

The definitions of response and timings of response assessment used for each of the biologics in the adult/adolescent model are summarised in Table 122 for patients not on mOCS and in Table 123 for patients on mOCS. As

highlighted above, these data reflect the proportions of patients achieving response among a population of patients examined in the respective pivotal trial of each comparator. In addition to the proportion of responders being based on alternative populations, they are based on alternative definitions of response; therefore, the data are not comparable. Appropriate caution is recommended when comparing against other biologics under a response assessment scenario. Data on proportion of responders were not reported for placebo, thus, comparisons between treatments are based on a naïve comparison.

The proportions of patients achieving response in more restricted (or reimbursed) populations are provided in Appendix R. Response Rates for Other Monoclonal Antibodies by Population (where reported).

Table 122. Response Assessment for Other Monoclonal Antibodies in Adult/Adolescent Model: Criteria, Timing and Proportions of Responders – Patients not on mOCS

Treatment	Response Definition	Review Timing (Weeks from First Administration)	% Responders	
			Mean	n
Omalizumab[a]	Physician's GETE	16 weeks	56.5%	118*
Mepolizumab[b]	improvement or stable exacerbation rates	52 weeks	90.9%	350

* Calculated using the number of patients in the omalizumab arm of the INNOVATE trial (209 patients).

a. Norman et al. 2013, Table 7;[61] based on ITT population from the INNOVATE trial

b. NICE TA479, Reslizumab – company evidence submission, Table 105 (page 190);(114) based on adult patients at GINA Step 4/5 with ≥ 2 exacerbations in the preceding year from the 3082 and 3083 studies

c. NICE TA431, Mepolizumab – company evidence submission, Table 104 (page 197);(112) based on ITT population from MENSA trial

Table 123. Response Assessment for Other Monoclonal Antibodies in Adult/Adolescent Model: Criteria, Timing and Proportions of Responders – Patients on mOCS

Treatment	Response Definition	Review Timing (Weeks from First Administration)	% Responders	
			Mean	n
Mepolizumab	Reduction in exacerbations	52 weeks	83.0%	83

* Calculated using the number of patients in the omalizumab arm of the INNOVATE trial (209 patients).

Source: NICE TA431, Mepolizumab – company response to appraisal consultation document (ACD),(66) Appendix 2, based on ITT population from MENSA trial restricted to maintenance OCS patients

Table 124. Response Assessment for Other Monoclonal Antibodies in Adult/Adolescent Model: Criteria, Timing and Proportions of Responders – Patients not on mOCS

Treatment	Response Definition	Review Timing (Weeks from First Administration)	% Responders	
			Mean	n
Omalizumab[a]	Physician's GETE	16 weeks	56.5%	118*
Mepolizumab[b]	Improvement or stable exacerbation rates	52 weeks	90.9%	350

* Calculated using the number of patients in the omalizumab arm of the INNOVATE trial (209 patients).

† Assumed based on the number of patients in the 3082 and 3083 studies (i.e., 477 patients in reslizumab arms).

Source:

a. Norman et al. 2013, Table 7;[61] based on ITT population from the INNOVATE trial

b. NICE TA431, Mepolizumab – company evidence submission, Table 104 (page 197);(112) based on ITT population from MENSA trial

Safety and Mortality Inputs

OCS-related Adverse Events

As risks of experiencing AEs were only applied to those who were steroid dependent, and OCS was not considered for the child population, AEs were only applicable to adult/adolescent patients. Alternative risks were applied to the proportion of patients requiring OCS treatment (i.e., those who did not withdraw completely as compared to those who did withdraw), based on the average OCS dose, assuming the risk of experiencing OCS-related AEs is constant over time.

AEs modelled in the adult/adolescent model were retained. Those were selected based on the availability of data.(115) The model considered the following AEs:

- Bone-related conditions
- Infections: severe infections, herpes zoster
- Metabolic disorders: hypertension, diabetes mellitus
- Ocular disorders: cataracts, glaucoma
- Gastrointestinal disorders: peptic ulcer
- Renal disorders: chronic kidney disease
- Psychiatric disorders: affective disorders
- Cardiovascular events

An overview of studies from the UK (as well as from the US) assessing the relationship between mOCS use and AEs in patients with asthma is provided in Appendix S. OCS-related Adverse Events – Sources Evaluated (for Adult/Adolescent Model). Most identified studies reported relative effects of experiencing AEs depending on OCS dose, OCS use or number of prescriptions. A systematic review of OCS-related AEs in the US and UK by Manson et al. (2009) was also identified.(116) That review identified several studies; however, these were not restricted to an asthmatic population and may be outdated.

A recently published CPRD study by Bloechliger et al. (2018) estimated the incidence rates of potential CS-related AEs in large cohorts (N's = 165,900 to 269,368) of patients with asthma.(117) This study represents one of the largest studies conducted to date investigating OCS-related AEs in an asthmatic population and it is recommended that the incidence rates of experiencing OCS-related AEs be informed based on this study in the base case. This includes the AE incidence rates among patients not receiving OCS (the "baseline risk" of AE; see Table 125) as well as the relative risks of experiencing AEs in patients receiving different doses of OCS as compared to not receiving OCS; Bloechliger et al. (2018) reported odds ratios for OCS use versus no OCS use (**Table 126**) for three different levels of OCS doses: ≤ 1 mg/day; > 1 – ≤ 5 mg/day; > 5 mg/day.(117)

Data based on an analysis of CPRD data conducted by GlaxoSmithKline (GSK) as part of the mepolizumab submission to NICE were also considered to inform the risk of OCS-related AEs.(64) The study by Bloechliger and colleagues was published in April 2018 and until then the GSK study seemed to represent the only study in asthmatic patients reporting incidence of AEs. However, limited details on the methods used were provided in the mepolizumab submission, and it received criticism regarding the fact that the relative risk of an event may not be linear in terms of magnitude of the dose of OCS (as GSK estimated relative risks of AEs due to additional gram of average cumulative OCS dose [per 28-day period] versus no OCS use). Due to the limitations associated with the GSK analyses, the study by Bloechliger et al. was considered more representative and used in the adult/adolescent model for dupilumab. Existence of Denmark-specific data on the frequency of AEs related to mOCS use was explored. However, as no appropriate data was identified, the UK data by Bloechliger et al. was used after confirming these data appear appropriate with Danish KOLs.

Table 125. Risk of Experiencing AEs in Patients Not Receiving OCS (UK Model)

	Incidence Rate per 100 Person-Years, Not on OCS	
AE	**Mean**	**SE**
Bone-related Conditions	1.21	0.02
Severe Infections	1.78	0.02
Herpes Zoster	0.47	0.01
Hypertension	1.19	0.02
Diabetes Mellitus	0.58	0.01
Glaucoma	0.17	0.01
Cataracts	0.59	0.01
Peptic Ulcer	0.09	0.00
Chronic Kidney Disease	0.98	0.01
Affective Disorders	0.89	0.01
Cardiovascular Events	0.47	0.01

Source: Calculated from Bloechliger et al. 2018, Table 3.(115) Incidence rates were divided by 10 to obtain values per 100 person-years and SEs were calculated based on the 95% CIs provided in the source, assuming a Normal distribution.

Table 126. ORs of Experiencing OCS-related AEs by Average Daily Dose of OCS versus No OCS Use (UK Model)

	OR of AE for Low-dose (≤ 1 mg/d) OCS vs No OCS Use			OR of AE for Medium-dose (> 1–≤ 5 mg/d) OCS vs No OCS Use			OR of AE for High-dose (> 5 mg/d) OCS vs No OCS Use		
AE	**Mean**	**95% CI Lower Limit**	**95% CI Lower Limit**	**Mean**	**95% CI Lower Limit**	**95% CI Lower Limit**	**Mean**	**95% CI Lower Limit**	**95% CI Lower Limit**
Bone-related Conditions	1.244	1.179	1.333	1.385	1.192	1.667	1.500	1.013	2.396
Severe Infections	1.985	1.924	2.061	3.036	2.670	3.251	2.433	1.773	3.258
Herpes Zoster	1.308	1.192	1.449	1.526	1.269	1.924	0.969	0.492	1.955
Hypertension	1.038	0.953	1.179	1.026	0.875	1.244	1.128	0.727	1.833
Diabetes Mellitus	1.308	1.205	1.436	1.538	1.308	1.955	1.621	0.914	2.944
Glaucoma	1.083	0.847	1.346	0.992	0.653	1.526	1.076	0.282	4.656
Cataracts	0.938	0.867	1.090	1.179	0.961	1.410	3.425	2.287	5.090
Peptic Ulcer	1.397	1.064	1.909	1.652	0.945	2.830	1.652*	0.945*	2.830*
Chronic Kidney Disease	1.167	1.077	1.282	1.128	0.969	1.346	1.621	1.077	2.440
Affective Disorders	1.423	1.308	1.667	1.636	1.231	1.985	2.803	1.591	5.050
Cardiovascular Events	1.321	1.192	1.462	1.462	1.179	1.879	0.953	0.435	2.248

Source: Bloechliger et al. 2018, Figure 2(115) The forest plot was imported into the Engauge Digitizer software (version 4.1). Since the horizontal scale varies across the plot (one can see for instance that the space between 0.2 and 0.5 is a lot larger than the space between 5 and 6), the data points had to be extracted in waves, with the axes reset after each wave. This was done as follows: 1) We began by identifying the points that fell between the x-axis values of 0.2 and 0.5 (the first interval on the plot). 2) We indicated to the digitizer tool where the points with the coordinates (0.2,0), (0.5,0) and (0.5,1) were located in the imported plot, and then we extracted those points with x-axis values between 0.2 and 0.5 and saved those values. 3) Next, we identified which points fell between 0.5 and 1 on the x-axis and we reset the digitization so that (0.5,0), (1,0) and (1,1) were being used to define the image scale. 4) Then we extracted those points that fell between the x-axis values of 0.5 and 1. This process was conducted six more times to extract the values that fell in the following ranges with regards to the x-axis: 1–1.5; 1.5–2; 2–3; 3–4; 4–5; 5–6. Once this was completed, all extracted data points with the same y-axis value were collated in order to be able to determine the mean OR and the limits of the CI of the OR for each AE and each OCS dose category (each corresponding to a different level on the y-axis).

* Assumed same as for the > 1–≤ 5mg/d category. No OR was reported by Bloechliger et al. 2018 for peptic ulcer for the > 5 mg/d category due to the very small number of patients involved.(115)

Fatality Rate Associated with Exacerbations Leading to Hospitalisation

As no additional data had been identified since the last severe asthma NICE technology appraisal during which asthma-related mortality was examined at length, the preferred committee assumption for that appraisal (benralizumab TA565)(65) was used in the base case in the final UK adult/adolescent model for dupilumab. These data, accepted by the committee and ERG in the NICE assessment of benralizumab, reflected the most conservative estimates used across models for asthma to date. They were based on data from Watson et al. (2007) (67), age-adjusted based on Roberts et al. (2013)(68), with further adjustment based on the most recent BTS

audit.(118) As no Danish data was identified regarding mortality related to asthma exacerbations, the same UK data is used in the Danish base case. Danish KOLs validated this approach.

In the benralizumab submission to NICE, fatality rates following a hospitalisation for severe exacerbation among the 45+ age group in the Watson et al. 2007 study (67) were adjusted based on the study by Roberts et al. 2013 (68). This adjustment was conducted as use of data by Watson has previously been criticised due to limited differentiation in mortality between patients aged 45-100. The exact calculation approach was not detailed in the submission; however, it is presumed that the odds ratios for the age groups 45–54, 55–64 and 65+ and the age distribution observed in the Roberts study were used to derive fatality rates within the 45+ group, whilst maintaining the average risk observed in the Watson study.

Mortality estimates were further adjusted thereafter for all age groups with the exception of patients aged 65+ years to align with the most recent estimates of mortality in the UK (119). Following the manufacturer's original submission, the ERG indeed criticised the mortality estimates used; specifically, these were considered to be unrepresentative based on recent evidence from the BTS asthma audit. The BTS audit conducted in 2016 reported that there were 33 deaths among 4,258 admissions of adult patients with asthma, corresponding to an average death rate of 0.0078 per hospital admission.(118) This average death rate per hospital admission implied by the combination of the Watson and Roberts studies was 0.01943, reflecting a 2.5 increase.(65) Fatality rates for all age groups (apart from 65+ years) were therefore divided by a factor of 2.5 by the ERG. The revised estimates (Table 40) were subsequently accepted by the NICE committee and were also used in the base case in the model for dupilumab.

Though data utilised in the benralizumab submission reflect the most conservative estimates used to date, fatality rates by age among patients aged 45+ years were deduced based on multiple sources. An updated analysis of the Camper Health Knowledge Systems (CHKS) database (similar to the Watson et al. study), including more granular age bands, was conducted in 2016 (120), including observations between 2000 and 2015. The average death rate among adults based on this updated analysis was 1.12% (see Appendix P for observed data), reflecting a 1.4 increase as compared to the BTS audit data (119). As the audit indicated that mortality rates remained stable among patients aged 75+ years, case fatality rates were adjusted by a factor of 1.6905 among patients aged 18–65 years to obtain an average rate of 0.78%. Use of these alternative estimates were examined in scenario analyses in the adult/adolescent model (Table 40). As the BTS asthma audit did not provide data for children nor adolescents(119) and in alignment with the approach described above with the base-case source (data from Watson et al. combined with Roberts et al., for which the same adjustment by 2.5 was applied for children and adolescents as was applied for adults), the same adjustment as for adults (i.e., by a factor of 1.6905) was applied to the CHKS data for patients aged 0–11 and 12–16 in order to derive the estimates used in this scenario analysis for children aged 6–11 and adolescents aged 12–17, respectively.

Adjustment of Other-cause Mortality based on Lung Function

In the adult/adolescent model, in the scenario where other-cause mortality was adjusted based on lung function, HRs of other-cause mortality by lung function level were based on a study conducted by Sanofi/Regeneron. Analyses were conducted to identify the influence of lung function on other-cause mortality (i.e., excluding death due to severe exacerbations) using the CPRD database (121). These analyses evaluated the influence of lung function on mortality, excluding death due to asthma, in patients hospitalised for asthma. A Cox proportional hazard model was fitted with moderate-severe asthma, aged 18 years or older, adjusted for age at index, smoking, body mass index (BMI), gender, rhinitis, chronic sinusitis, nasal polyps, atopic dermatitis, diabetes, anaphylaxis, ischaemic heart disease, heart failure, food allergy, anxiety, depression and psoriasis. HRs were obtained for the following three categories of ppFEV1: ppFEV1 ≥ 80% (reference category), ppFEV1 between 50% and 79%, and ppFEV1 < 50% (Table 127).

Table 127. HRs for Other-cause Mortality by ppFEV$_1$ Level

ppFEV$_1$ Level	Hazard Ratio		
	Mean	**95% CI Lower Limit**	**95% CI Upper Limit**
≥ 80%	1.000		
50%–79%	1.862	1.606	2.159
< 50%	2.919	2.468	3.452

Source: CPRD analysis, Sanofi/Regeneron data on file(121)

Based on these distributions and on the HRs associated with the different levels of ppFEV1, HRs were calculated for each treatment (as a weighted average of the proportions of patients in each ppFEV1 category and of the HRs corresponding to each category) compared to a cohort of patients with ppFEV1 ≥ 80% (Table 128).

Table 128. HRs of Other-cause Mortality by Treatment as Compared to a Cohort of Patients with ppFEV$_1$ ≥ 80%

	LIBERTY ASTHMA QUEST – EMA Population	LIBERTY ASTHMA VENTURE – EMA Population
Dupilumab + Background Therapy (All Patients)	1.819	1.941
Responders – Based on Improvement in Exacerbation Risk	1.765	1.911
Responders – Based on Decrease in OCS Dose	NA	1.863
Background Therapy Alone	1.031	2.202

* Example calculation: 23.35% x 1.000 + 61.68% x 1.862 + 14.79% x 2.919 = 1.819

Data presented in Table 128 were then expressed versus the general population using assumptions. As described in Appendix P. Implementation of Impact of Lung Function on Other-cause Death in Adult/Adolescent Model, three different approaches to this normalisation were included in the adult/adolescent model:

1. Assume other-cause mortality risk in patients treated with background therapy is equivalent to the general population
2. Assume other-cause mortality risk in patients treated with the monoclonal antibody associated with the largest improvements in FEV$_1$ is equivalent to the general population
3. Consider ppFEV$_1$ data for the general population and estimate HR versus general population

The HRs obtained (for all patients and for responders) with these different approaches are summarised in Table 129. These normalised HRs were then applied to the other-cause mortality rates observed in the general population for each respective treatment.

We considered that the most appropriate approach to derive excess mortality versus the general population would involve considering the distribution of ppFEV1 in the general population (the third option); however, this option is hampered by data availability. Generally, studies evaluating lung function focus on patients with respiratory diseases; thus, limited data—if any—were identified to inform these inputs based on a pure general population. Nonetheless, to determine the potential influence of using data from a general population, the distribution of the UK general population in terms of ppFEV1 was estimated based on an older Danish study by Lange and colleagues (1998) (as presented in Table 130 (122). Given the data were outdated, do not reflect a UK population and were based on a population without lung disease, all assumptions were examined in scenario analysis in the adult/adolescent model.

Table 129. Normalised HRs of Other-cause Mortality by Treatment – Expressed versus UK Adult/Adolescent Population

	LIBERTY ASTHMA QUEST – EMA Population	LIBERTY ASTHMA VENTURE – EMA Population
Assume Other-cause Mortality Risk in Patients Treated with Background Therapy is Equivalent to the General Population		
Dupilumab + Background Therapy (All Patients)	0.925	0.882
Responders – Exacerbation Reduction	0.897	0.868
Background Therapy Alone	1.000	1.000
Assume Other-cause Mortality Risk in Patients Treated with the Monoclonal Antibody Associated with the Largest Improvements in FEV_1 Is Equivalent to the General Population*		
Dupilumab + Background Therapy (All Patients)	1.031	1.016
Responders – Exacerbation Reduction	1.000	1.000
Background Therapy Alone	1.114	1.152
Include $Ppfev_1$ Data for the General Population and Estimate HR Versus General Population		
Dupilumab + Background Therapy (All Patients)	1.488**	1.588
Responders – Exacerbation Reduction	1.444	1.564
Background Therapy Alone	1.609	1.802

* Note that in the model, only one response rule is considered at a time; therefore, the normalised HR estimated in this scenario would vary based on the response definition selected.
** Example calculation: 1.819 (Table 128) / 1.222 (see footnote underneath Table 130) = 1.488

Table 130. Distribution of $ppFEV_1$ in the Adult/Adolescent Population

$ppFEV_1$ Level	General Population
≥ 80%	75.68%
50%–79%	23.14%
< 50%	1.182%

Source: Calculated from Lange et al. 1998;(122) data for patients without asthma; HR of the general population versus a cohort of patients with $ppFEV_1 \geq 80\%$ would be 75.68% x 1.000 + 23.14% x 1.862 + 1.182% x 2.919 = 1.222

Appendix N. Calculations of Relative Risks for Responders to Other Monoclonal Antibodies (Adult/Adolescent Model)

Mepolizumab Responders

The model used in the mepolizumab submission to NICE included three types of clinically significant exacerbations: exacerbations requiring treatment with OCS, exacerbations requiring an ER visit, and exacerbations requiring hospitalisation.(112) That model used a single event rate for all clinically significant exacerbations and then used the respective proportions of the three different types (based on trial data) to distribute the exacerbations by type. Table 131 below summarises the various RRs (in terms of clinically significant exacerbation rates) for mepolizumab responders versus SoC, corresponding to the populations explored in the submission. The following section describes the rationale and the methods used to derive these estimates of relative efficacy. For our model, it was assumed that rates of clinically significant exacerbations would be applicable to severe exacerbations in the model.

The following three populations were included in the submission of mepolizumab to NICE (see Table 99 in the company evidence submission(112)):

1. **"Mepolizumab modified ITT population":** ITT population (defined by the inclusion criteria of the MENSA trial). Patients have a blood eosinophil count ≥ 150 cells/µL at initiation of treatment or a blood eosinophil count ≥ 300 cells/µL in the prior 12 months, who experience ≥ 2 exacerbations in the previous year. This population was used in the company's base-case analysis and in the comparison against omalizumab. This population was used in our base-case analysis for the "Mepolizumab-like population".

2. **"Mepolizumab company proposed population": Patients who have a blood eosinophil count of ≥ 150 cells/µL at initiation of treatment; and ≥ 4 exacerbations in the previous year or dependency on maintenance OCS.**

3. **"Mepolizumab company proposed population excluding OCS users with < 4 exacerbations in the previous year": Patients have a blood eosinophil count ≥ 150 cells/µL at initiation of treatment; and ≥ 4 exacerbations in the previous year.**

In addition, in the response to the appraisal consultation document data were provided for the ITT population restricted to maintenance OCS, used for comparisons versus steroid dependent populations.

The mean annual exacerbation rates (and SEs) for SoC and for mepolizumab responders for these three populations were reported in Table 126 in the company evidence submission(112) and are included in the first three rows of Table 131 below.

Table 131. Relative Risk of Clinically Significant Exacerbations for Mepolizumab Responders versus SoC based on the NICE Appraisal of Mepolizumab

Comparator	SoC—Annual Rate (SE)	Mepolizumab, Post-continuation Assessment—Annual Rate (SE)	Relative Rate (SE)
Mepolizumab (modified ITT population)	1.7439 (0.09773)*	0.5504 (0.1459)*	0.316 (0.271)
Mepolizumab (company proposed population)	2.65 (0.157)*	0.6447 (0.2238)*	0.243 (0.352)
Mepolizumab (company proposed population excluding OCS users with < 4 exacerbations in the previous year)	3.1005 (0.1795)*	0.7232 (0.2316)*	0.233 (0.325)
Mepolizumab (ITT restricted to maintenance OCS)	2.120 (0.109)**	0.990 (0.215)	0.467(0.150)

Sources:

* Table 126 in the company evidence submission (112). ** Appendix 2 in company response to appraisal consultation document; SEs were not reported, however, approximated based on N=83 responders in the mepolizumab responders and assuming N=46 based on 191 patients randomised to placebo in MENSA and 24% of patients receiving maintenance OCS. Number of events approximated by multiplying rate times number of patients in each arm.

Relative Rates

Mean RRs for the three populations were calculated by dividing the annual rate of exacerbation for mepolizumab responders by the annual rate of exacerbation for patients on SoC. CIs for these mean RRs were calculated using the following formula:

$$95\%\ CI = e^{\left(\ln(RR) \pm z_{0.975}\sqrt{\frac{1}{a}+\frac{1}{b}}\right)}$$

where $RR$is the mean relative rate, $z_{0.975}$ is the z-score for the 97.5th percentile of the standard normal distribution (≈ 1.96), a is the number of exacerbation events that patients randomised to SoC experienced and b is the number of exacerbation events that mepolizumab responders experienced. a (and similarly, for b) is calculated by the following formula:

$$a = \left(\frac{r}{SE(r)}\right)^2$$

where r is the mean exacerbation rate and $SE(r)$ is the SE of the mean exacerbation rate. The text below provides further explanations about this formula.

This formula assumes that the number of exacerbations (noted D below) during a period follows a Poisson distribution, which is equivalent to assuming that the time to event is constant (time to exacerbation is assumed to be exponentially distributed). A limitation of this assumption is that it does not consider the change in exacerbation risk given a patient had an exacerbation. Writing the likelihood $P(D)$ of the number of events D, we have:

$$P(D) = \frac{(rT)^D e^{-rT}}{D!}$$

where r is the event rate per patient-year of exposure and T is the number of patient-years of exposure. Writing the log-likelihood ll, we have:

$$ll = Dln(rT) - rT - \ln(D!)$$

Taking the derivative of the log-likelihood with respect to r and setting it equal to zero to maximise the log-likelihood, we have:

$$\frac{\delta ll}{\delta r} = \frac{D}{r} - T = 0$$

The maximum likelihood estimate for the expected value of r is then:

$$E[r] = \frac{D}{T}$$

The variance of the mean estimate is then:

$$Var[E[r]] = Var\left[\frac{D}{T}\right] = \frac{1}{T^2}Var[D] = \frac{1}{T^2}E[D] = \frac{rT}{T^2} = \frac{r}{T}$$

since the mean and the variance of Poisson-distributed random variables are the same (= rT). r is estimated as $\frac{D}{T}$, therefore the standard error of r can be written as:

$$SE(r) = \frac{\sqrt{D}}{T}.$$

Given the mean and SE of r, we can use $D = \frac{r^2}{SE(r)^2}$ to get the number of events, which we can then use in the formula for calculation of the CI of the RR.

Appendix O. Estimation of Transition Probabilities

The transition probabilities in the adult/adolescent model were estimated in the form of a transition probability matrix P (or transition matrix), whose elements Pij-s represent the estimated probabilities from transitioning from state i to state j, where i and j are members of the given set of health states. As an illustration, the transition matrix of the five-sub-state model is depicted in Table 132 where the starting states are presented by different rows and states of transitions are presented by different columns. Probabilities in each row must add up to one. Transitions are allowed from any state to any state.

Table 132. Five-Sub-State Transition Probability Matrix

From (*i*) / To (*j*)	Uncontrolled Asthma	Controlled Asthma	Moderate Exacerbation	Severe Exacerbation	Sum
Uncontrolled Asthma	$P_{1,1}$	$P_{1,2}$	$P_{1,3}$	$P_{1,4}$	$\sum P_{1,j}=1$
Controlled Asthma	$P_{2,1}$	$P_{2,2}$	$P_{2,3}$	$P_{2,4}$	$\sum P_{2,j}=1$
Moderate Exacerbation	$P_{3,1}$	$P_{3,1}$	$P_{3,3}$	$P_{4,2}$	$\sum P_{3,j}=1$
Severe Exacerbation	$P_{4,1}$	$P_{4,2}$	$P_{4,3}$	$P_{4,4}$	$\sum P_{4,j}=1$

Estimating Transition Probabilities

As the model cycle's length was four weeks, all transition probability matrices were calculated for four weekly transitions. The transition probability estimation involves counting the number of patients in each health state across the relevant time periods, along with the frequency of transitions to other health states from that health state across the same time periods.

To estimate transition probabilities of a given subgroup, all transitions between health states (observed or imputed) were counted during a given period. Four-week jumps were collected to a transition frequency matrix (for an illustration, see Table 133).

Table 133. Five-Sub-State Transition Frequency Matrix

From (*i*) / To (*j*)	Uncontrolled Asthma	Controlled Asthma	Moderate Exacerbation	Severe Exacerbation	Sum
Uncontrolled Asthma	$N_{1,1}$	$N_{1,2}$	$N_{1,3}$	$N_{1,4}$	$\sum N_{1,j}= N_1$
Controlled Asthma	$N_{2,1}$	$N_{2,2}$	$N_{2,3}$	$N_{2,4}$	$\sum N_{2,j}= N_2$
Moderate Exacerbation	$N_{3,1}$	$N_{3,1}$	$N_{3,3}$	$N_{4,2}$	$\sum N_{3,j}= N_3$
Severe Exacerbation	$N_{4,1}$	$N_{4,2}$	$N_{4,3}$	$N_{4,4}$	$\sum N_{4,j}= N_4$

The maximum likelihood estimate of the transition probability matrix is the matrix of relative frequencies. Namely, the counts of transitions (Ni,j) in each row (for any i) are divided by the total sum of transitions $\sum$ Ni,j= Ni in that row (row i). Transition probabilities are estimated as Pi,j=Ni,j/Ni for any i,j=1,...,4. The total number of transitions in each row (Ni) is provided along with the estimated probabilities (Pi,j) for all matrices that are estimated.

Transition probabilities were calculated from transitions of patients while they were on randomised treatment (i.e., transitions of patients after they permanently discontinue the randomised treatment were not included in the calculation of the number of transitions).

A similar approach to estimating transition probabilities was applied for the children data from the LIBERTY ASTHMA VOYAGE trial.

Appendix P. Implementation of Impact of Lung Function on Other-cause Death in Adult/Adolescent Model

The adult/adolescent model for dupilumab included an option to consider the impact of lung function on other-cause mortality, thus allowing to use the differences observed between treatments in terms of lung function improvements to determine different mortality rates for each treatment.

In this instance, general population life tables were adjusted based on lung function levels for each treatment (see details in the Adjustment of Other-cause Mortality based on Lung Function section), expressed in terms of FEV1 as a percentage of predicted (ppFEV1), and it was assumed that the differences in ppFEV1 between treatments remain constant whilst patients are on the treatment.

A hazard ratio (HR) of other-cause mortality was estimated for each treatment, based on the distribution of patients across different levels of ppFEV1 (≥80%; 50%–79%; <50%) and the HR of other-cause mortality for each of these three different categories of ppFEV1 levels (details are provided in the Adjustment of Other-cause Mortality based on Lung Function section).

These HRs obtained for the different treatments were then normalised via the use of assumptions to determine the excess mortality of the population and treatment modelled as compared to the general population. The possible assumptions considered were:

- Other-cause mortality risk in patients treated with background therapy is equivalent to the general population: Excess mortality versus the general population for the monoclonal antibodies is estimated by dividing the calculated HR of mortality for patients treated with the monoclonal antibodies (compared with a cohort with ppFEV1>80%) by the HR of mortality for patients treated with background therapy (compared with a cohort with ppFEV1>80%). This assumption would result in a lower other-cause mortality risk compared with the general population for patients treated with monoclonal antibodies.
- Other-cause mortality risk in patients treated with the monoclonal antibody associated with the largest improvements in FEV1 is equivalent to the general population: This assumption would result in an equivalent other-cause mortality risk to the general population for patients treated with monoclonal antibody associated with the largest improvement in FEV1. Excess mortality versus the general population for other treatments is estimated by dividing the implied HR of mortality for patients treated with the comparator (compared with a cohort with ppFEV1>80%) by the HR of mortality for patients treated with the reference therapy (compared with a cohort with ppFEV1>80%).
- Include ppFEV1 data for the general population and estimate HR versus the general population: This is the most appropriate assumption; however, this option is hampered by data availability. Generally, studies evaluating lung function focus on patients with respiratory diseases; thus, limited data—if any—are anticipated to inform these inputs based on a pure general population. Subject to availability of ppFEV1 values in the general population, excess mortality versus the general population is estimated by dividing the implied HR of mortality for patients treated with the comparator (compared with a cohort with ppFEV1>80%) by the HR of mortality for the general population (compared with a cohort with ppFEV1>80%).

The normalised HRs were then applied to the other-cause mortality data obtained from life tables for each treatment separately. For monoclonal antibodies, two separate HRs were estimated for all patients and for responders only, similarly to the approach used for efficacy outcomes. Therefore, different HRs were used for the period prior to and after response assessment.

Appendix Q. Deriving Transition Probabilities for Other Monoclonal Antibodies

In the adult/adolescent model, transition probabilities between the live health states were obtained from the LIBERTY ASTHMA QUEST (patients not on OCS) and VENTURE (patients on OCS) trials for dupilumab and for background therapy alone (see section with transition probabilities). In order to derive transition probabilities for the other monoclonal antibodies, their RRs were applied to the transition rates associated with dupilumab following the process described further below.

- The transition probability to severe exacerbation was first calculated. If we consider an example where we estimate the transition probabilities for mepolizumab (all patients), the transition probability to severe exacerbation was calculated as:

$$(P_{i,SevExac})_{Mepo} = 1 - \exp\left(-RR_{SevExac_{MepoVs.Dupi}} \times \left(R_{i,SevExac}\right)_{Dupi}\right)$$

  where $(P_{i,SevExac})_{Mepo}$ is the probability of transitioning to the 'Severe Exacerbation' state from a given state i for mepolizumab patients, $(R_{i,SevExac})_{Dupi}$represents the same transition rate for dupilumab patients (estimated as $1 - \ln\left(1 - \left(P_{i,SevExac}\right)_{Dupi}\right)$, and $RR_SevExac_{MepoVs.Dupi}$is the relative rate of experiencing severe exacerbation for mepolizumab compared to dupilumab.

  If this operation resulted in a value greater than 1, then the transition probability to severe exacerbation for mepolizumab was restricted to 1.

- The probability of transitioning to moderate exacerbation from the same given state i was then calculated, in the same manner, using the RR of experiencing moderate exacerbations for mepolizumab versus dupilumab:

$$(P_{i,ModExac})_{Mepo} = 1 - \exp\left(-RR_{ModExac_{MepoVs.Dupi}} \times \left(R_{i,ModExac}\right)_{Dupi}\right)$$

- Likewise, the transition probability to moderate exacerbation for mepolizumab was restricted to $1 - (P_{i,SevExac})_{Mepo}$(this ensures that $(P_{i,ModExac})_{Mepo} + (P_{i,SevExac})_{Mepo}$cannot be greater than 1).

- In the four-sub-state model, the probability of transitioning to the 'No exacerbation' state from the same given state i was then obtained simply as:

$$(P_{i,NoExac})_{Mepo} = 1 - (P_{i,ModExac})_{Mepo} - (P_{i,SevExac})_{Mepo}$$

- In the five-sub-state model:

  - The probability of transitioning to the 'Uncontrolled asthma' state from the same given health state i was obtained in a similar manner:

$$(P_{i,Uncontr})_{Mepo} = 1 - \exp\left(-RR\_Uncontr_{MepoVs.Dupi} \times (R_{i,Uncontr})_{Dupi)}\right)$$

  Again, this transition probability to the 'Uncontrolled asthma' state was restricted so that it could not be greater than $1 - (P_{i,SevExac})_{Mepo} - (P_{i,ModExac})_{Mepo}$.

  - The probability of transitioning to the 'Controlled asthma' state from the given state i was then simply obtained as:

$$(P_{i,Contr})_{Mepo} = 1 - (P_{i,Uncontr})_{Mepo} - (P_{i,ModExac})_{Mepo} - (P_{i,SevExac})_{Mepo}$$

Appendix R. Response Rates for Other Monoclonal Antibodies by Population

Table 134. Proportion of Patients Achieving Response with Mepolizumab

Population	% Responders	n/N	Criteria	Source
ITT population	90.9%	350/385	Patients who experience an increase in annualised exacerbation rate are discontinued	NICE TA431, company evidence submission, Table 104 (based on MENSA trial)
Company proposed population excluding OCS users with < 4 exacerbations: EOS ≥ 150 cells/µl; ≥ 4 exacerbations	97.1%	99/102		
Company proposed population: EOS ≥ 150 cells/µl; ≥ 4 exacerbations in previous year or dependency on OCS	92.3%	132/143		
ITT population restricted to maintenance OCS patients	83.0%	83/100	Patients for whom exacerbation rate improves	NICE TA431, company response to ACD, Appendix 2 (based on MENSA trial)
≥ 4 exacerbations in previous year or dependency on OCS	89.5%	170/190		
EOS ≥ 300 cells/µl; ≥ 4 exacerbations in previous year or dependency on OCS	89.2%	157/176		
EOS ≥ 300 cells/µl in previous year; ≥ 4 severe exacerbations in previous year or dependency on OCS (reimbursed population)	76.7%	122/159	≥ 50% reduction in exacerbation rate versus baseline*	NICE TA431, company response to the second ACD, Table 9 (based on MENSA trial)
	84.3%	134/159	≥ 30% reduction in exacerbation rate versus baseline	

* Continuation criterion specified in FAD for mepolizumab, alongside clinically significant reduction in continuous OCS use while maintaining or improving asthma control.

Table 135. Proportion of Patients Achieving Response with Omalizumab

Population	% Responders	Confidence Interval	Trial
ITT population	56.5%	49.7%–63.2%	INNOVATE*
	69.9%		EXALT‡
	82.4%		APEX†
Patients who experienced a hospitalisation for asthma in the year prior to enrolment in the study	56.6%	46.0%–67.3%	INNOVATE*
	56.9%		EXALT‡
	82.7%		APEX†
Patients receiving maintenance OCS at randomisation	46.9%	33.0%–60.9%	INNOVATE*
	52.5%		EXALT‡
	78.9%		APEX†
≥ 3 exacerbations in previous year	46.5%	36.0%–57.1%	INNOVATE*

NICE recommendation: people aged 6 or older who need continuous or frequent treatment with OCS (defined as 4 or more courses in the previous year).

*Double-bind, ‡Open label, †Observational

Source: Norman et al. (2013), Tables 49, 65 and 96. Assessment of response based on reported GET

Appendix S. OCS-related Adverse Events – Sources Evaluated (for Adult/Adolescent Model)

Table 136. Published Studies in the UK and US Assessing Influence of OCS on Risk of Adverse Events

Reference	Country	Database	Sample	Enrolment/ Follow-up	Population	Control Variables	Outcomes	Challenge

Bloechliger 2018(115)	UK	CPRD	165,900–269,368	2000–2015	Patients aged 18 years or older with incident or prevalent asthma requiring at least GINA Step 2 treatment	• Non-OCS users
						• Ever users
						• Current users
						  • Average daily dose ≤ 1 mg
						  • Average daily dose > 1–≤ 5 mg
						  • Average daily dose > 5 mg
							Incidence and ORs for control variables for:
							• Bone-related conditions
							• Hypertension
							• Peptic ulcer
							• Severe infections
							• Herpes zoster
							• Diabetes mellitus
							• Cataract
							• Glaucoma
							• Chronic kidney disease
							• Affective disorders
							• Cardiovascular events
								• Inputs required on QoL and costs

Mepolizumab submission to NICE, 2016(64)	UK	CPRD	Not reported	2004–2012	Severe asthma patients defined by GINA guidelines Step 4/5	Additional gram of average cumulative maintenance OCS dose (over 28-day period) versus no use	Relative risk of event due to additional gram of average cumulative maintenance OCS dose (over 28-day period) versus no OCS use, for: • Diabetes • Myocardial infarction • Osteoporosis • Peptic ulcer • Cataract	• Inputs required on QoL and annual risk of events • Limited details on methods
Sweeney 2016(123)	UK	British Thoracic Society Difficult Asthma Registry	Severe asthma: 770	Not reported	GINA Step 5 treatment and ≥ 4 prescriptions for OCS in each of two consecutive study years	• CS-dependent asthma • Required daily systemic CS therapy to maintain asthma control • Non-CS dependent asthma	ORs for: • Endocrine disorder • Cardiac disease • Osteoporosis • Obesity • Sleep disorders • Eye diseases • Dyspeptic disorders • Psychiatric disorders • Skin conditions Specific conditions within each category listed	• May not capture benefit of dose reduction (only withdrawal) • Inputs required on QoL and annual risk of events

Walsh 2001(124)	UK	Questionnaire to 41 general practices close to Nottingham	451	Not reported	Men and women aged 50 years or more with a diagnosis of asthma, COPD, or fibrosing alveolitis if they required either (a) continuous OCS, defined as daily or alternate day OCS therapy for at least the last 6 months or (b) frequent intermittent courses of OCS, defined as a mean daily dose of 5 mg prednisolone (or equivalent dose of other corticosteroid) over the previous 6 months	• Patient taking OCS and evaluated by quartile (mean cumulative gram) • Corticosteroid quartile 1: 5.1 (1.1–7.7) • Corticosteroid quartile 2: 11.7 (7.8–16.3) • Corticosteroid quartile 3: 23.6 (16.4–37.4) • Corticosteroid quartile 4: 60.6 (37.6–186) • Control patients	OR for steroid-dependent (also by quartile) versus control: • All fracture • Vertebrae • Ribs sternum • Cataract • Bruising • Muscle weakness	• Not specific to an asthma population • Not all potential OCS-related AEs captured • Evidence may be outdated
Manson 2009(116)	UK	Literature search	Not applicable	Studies published between 1990–2007	Papers measuring prevalence of OCS adverse effects among oral steroid users, the relationship between the presence of OCS side effects and patient characteristics such as treatment history, age, gender, or	Not applicable	Cost per patient year of OCS-related AE	• Literature search not specific to asthma or population of interest • Evidence may be outdated

					duration of steroid use, the dose-response relation-ship			
Zazzali 2015(125)	US	Commercial health care claims	37,123	2008–2009	Patients ≥ 18 years of age who had ≥ 2 medical claims with asthma as one of the listed diagnoses and had filled ≥ 2 asthma medications	• High OCS • Patients with ≥ 30 annual days of supply (cumulative annual dose 1,260 mg) • No OCS • Patients with < 30 annual days of supply (cumulative annual dose 250 mg)	Risk of AEs in patients with no OCS versus high OCS: • Any AE • Bone-related conditions • Osteoporosis • Fractures • Pneumonia • Opportunistic infections • Hypertension • Diabetes • Glaucoma • Cataracts • Lipid disorders • Obesity • Peptic ulcer disease	• May not capture benefit of complete withdrawal • Inputs required on QoL • Not specific to patients with uncontrolled persistent asthma
Lefebvre 2017(126)	US	Medicaid claims data	SGC users: 3,628 No SGC: 26.987	1997–2013	> 12 years of age, with > 2 administrative claims associated with an asthma diagnosis (ICD-9-CM code 493.xx)	• SGC users: chronic SGC use of ≥ 6 months duration (defined as ≥ 5 mg daily prednisone dose equivalent with no gap between two SGC claims ≥ 14 days) • Low SGC exposure: ≤ 6 mg/day • Medium SGG exposure: >6–<12 mg/day • High SGC exposure: ≥ 12 mg/day • No SGC	OR for complications versus no SGC: • Gastrointestinal • Infections • Bone- and muscle-related • Cardiovascular • Haemato-logic/onco-logic • Metabolic • Ocular • Psychiatric • OR for resource use versus no SGC: • ER visit • Outpatient visit • Inpatient visit • Pharmacy dispensing • Other visit Annual incremental costs and costs associated with incidence of complications	• Inputs required on QoL and annual risk of events • Not specific to patients with uncontrolled persistent asthma
Sullivan 2017(127)	US	MarketScan	Before matching	2000–2014	Asthmatic patients aged 18 years and older with continuous	OCS prescriptions: • Current 1–3 prescriptions • Current ≥ 4 prescriptions	OR for incident new AE and for: • Osteoporosis • Fracture • Metabolic syndrome	• No regard to dose or duration of OCS • Inputs required on QoL

OCS cohort: 72,603 No OCS cohort: 156,373	enrolment for 12 months or more before and 24 months or more after the index date	• No. of prior years with 1–3 prescriptions • No. of prior years with ≥ 4 prescriptions • No. of years with 1–3 prescriptions • No. of years with ≥ 4 prescriptions	• Hypertension • Obesity • Type 2 diabetes • Dyslipidaemia • Avascular necrosis • Gastrointestinal ulcers/bleeds • Tuberculosis • Cataract • Glaucoma	and annual risk of events • Not specific to patients with uncontrolled persistent asthma

Appendix T. Asthma-related Mortality

Sources Evaluated to Inform Asthma-related Mortality in UK Adult/Adolescent Model

Table 137. Studies Assessing Mortality after a Hospitalisation or Exacerbation (UK and US)

Ref	Country	Years Of Enrolment	Population	Database	Outcome Data	Stratification	Results	Challenge
Watson 2007(67)	UK	2000–2005	Patients hospitalised under ICD-10 codes J45 ("asthma") and J46 ("acute severe asthma") between April 2000 and March 2005	Camper Healthcare Knowledge Systems (CHKS) database	Proportion of deaths in patients with asthma-related admission (for ICD-10 code J45 and for code J46)	By age band (<12, 12–16, 17–44 and ≥45 years)	Results presented per 100 acute severe asthma admissions by age group -0–11: 0.97 (0.42–1.91) -12–16: 0.319 (0.104 – 0.742) -17–44: 0.383 (0.267 – 0.529) - 45+: 2.478 (2.129 – 2.865)	Data provided for acute severe asthma admission, requiring external sources to inform mortality in non-hospitalised severe exacerbations Death may not necessarily be attributed to asthma exacerbation Population is not restricted to patients with uncontrolled persistent asthma Data provided for age group ≥45 years, requiring

								assumptions or external data to inform variation in mortality above the age of 45
CHKS updated analysis 2016**(120)**	UK	2000–2015	All patients admitted (emergency admission only) with specific asthma-related code J46 ("acute severe asthma"; status asthmatics) as primary reasons their first episode within a spell were included, within the time period April 1, 2000–March 31, 2015	CHKS database	Asthma-related mortality post admission	By age band (0–11, 12–16, 17–44, 45–54, 55–64, ≥65 years)	0–11: 0.07% 12–16: 0.18% 17–44: 0.30% 45–54: 0.92% 55–64: 1.52% 65+: 4.55%	Population is not restricted to patients with uncontrolled persistent asthma Death may not necessarily be attributed to asthma exacerbation Limited information on methodology
De Vries 2010**(69)**	UK	1993–Not reported (average follow-up 5 years)	Patients aged ≥18 years who received a prescription for inhaled SABA or LABA after 1 January 1993. Patients coded as COPD were excluded.	UK General Practice Research Database (GPRD), linked to the national registry of hospital admission (hospital episode statistics [HES])	Incidence rates of asthma death for status asthmaticus during current exposure	By treatment step (using the BTS/SIGN guidelines of 2005)	Asthma death rate between 0.01 and 0.4 per 100 person-years, depending on treatment step	Rates of death are not reported specifically for patients with exacerbations, rather by treatment step Classification of patients based on BTS/SIGN guidelines in 2005,

								which varies from 2017 guidance
Roberts 2013**(68)**	Scotland	1981–2009	All asthma hospitalisations for adults (>18 years) with ICD-9 code 493 and ICD-10 codes J45-J46 in the principal diagnostic position at discharge (1981–2009)	Scottish Morbidity Record Scheme (SMR01) linked to General Register Office for Scotland (GROS)	Odds ratio for 30-day case-fatality after asthma admission	Odds ratio by age band (18–24, 25–34, 35–44, 45–54, 55–64, ≥65 years)	Crude 30-day case-fatality rate of 0.9%. Based on odds ratios and distribution of cohort, this implies a risk between 0.20%–2.52% depending on age	Death may not necessarily be attributed to asthma exacerbation Data provided for asthma admission, requiring external sources to inform mortality in non-hospitalised severe exacerbations Population is not restricted to patients with uncontrolled persistent asthma
Sheikh 2016**(128)**	Scotland	2001–2010	Not reported	NHS Scotland hospital discharge and death records (Scottish Health and Ethnicity Linkage Study)	Risk of death	Not applicable	Death was an infrequent occurrence 0.4% of first asthma events	Data not provided by age group Death may not necessarily be attributed to asthma exacerbation Population is

								not restricted to patients with uncontrolled persistent asthma
Kaur 2015**(129)**	US	2001–2010	Patients with a primary diagnosis of asthma (ICD-9-CM code: 493)	Nationwide Inpatient Sample (NIS) database between 2001–2010	In-hospital mortality	By age 5–14, 15–34, 35–54, 55–74, 75+	In-hospital mortality by age: - 5–14: 0.08% -15–34: 0.26% -35–54: 0.49% -55–74: 1.35% -75+: 3.02%	Death may not necessarily be attributed to asthma exacerbation Data provided for asthma admission, requiring external sources to inform mortality in non-hospitalised severe exacerbations Population is not restricted to patients with uncontrolled persistent asthma
Sullivan 2009**(130)**	US	Not reported	Severe asthma patients, hospitalised for asthma	Closed panel health maintenance organisation	30-day risk of death following hospitalisation or exacerbation for asthma	Not applicable	30-day risk of death following hospitalisation for asthma was 2.48% (0.5%–7.1%)	Only available in abstract form with limited details on methodology Age distribution

							and following an exacerbation was 1.1% (0.2%–3.1%)	of patients or risks by age are not provided
Krishnan 2006(131)	US	2000	Hospital admissions with a primary discharge diagnosis of asthma or respiratory failure with secondary diagnosis of asthma	Nationwide Inpatient Sample (NIS) 2000 data	In-hospital mortality	By age 5–14, 15–34, 35–54, 55–74, 75+	Overall hospital mortality for asthma exacerbations was 0.5% (0.4%–0.6%). By age: - 5–14: 0.02% -15–34: 0.2% -35–54: 0.3% -55–74: 0.8% -75+: 1.9%	Data may be outdated and appears to be at the lower spectrum as compared to other published literature Death may not necessarily be attributed to asthma exacerbation Data provided for asthma admission, requiring external sources to inform mortality in non-hospitalised severe exacerbations Population is not restricted to patients with uncontrolled

Asthma-related Mortality in Previous Models

Economic evaluations identified as part of the SLR for the adult/adolescent model were further reviewed to determine inputs used to inform the fatality rates associated with exacerbations. Previous models generally assumed that the rate of death due to exacerbations was independent of age, with values ranging between 0.043%–3.11%. Lower estimates of 0.1%(61) and 0.043%(87) reported in these models are unlikely to be applicable as they are based on rates of asthma death in patients treated with OCS rather than probability of death after an exacerbation(69) and a converted per-cycle risk (rather than per event).(87)

Table 138. Input Values Used to Model Death due to Exacerbation in Previous Models

Study	Fatality rate associated with exacerbation	Applied to	Source
Institute for Clinical and Economic Review, 2015**(63)**	2.48%	Severe exacerbations leading to hospitalisation	Watson et al., 2007(67)
Institute for Clinical and Economic Review, 2018**(132)**	1.79%	Exacerbation-related ED visits	NRAD 2014(70)
	2.48%	Exacerbation-related hospitalisation	Watson et al., 2007(67)
Norman et al., 2013**(61)**	0.1%	Severe exacerbations	de Vries et al., 2010(69)
Brown et al., 2007**(133)**	3.11%	Severe exacerbations	Lowhagen et al., 1997(134)
Campbell et al., 2010**(85)**	1.10%	Severe exacerbations leading to hospitalisation	Sullivan et al., 2009(130)
Dewilde et al., 2006**(135)**	2.08%	Severe exacerbations	Lowhagen et al., 1997(134) and assumptions based on INNOVATE trial
Lam et al, 2018**(136)**	1%	In-hospital mortality rate from an exacerbation	Kaur et al, 2015(137)
Morishima et al., 2013**(138)**	1.55%	Unclear	Japanese Vital statistics
Nguyen et al., 2017**(87)**	0.043%	Severe exacerbations	Sullivan et al., 2009(130)
Sullivan et al, 2020**(139)**	1.8%	Exacerbation requiring emergency room visit	NRAD 2014(70)
	2.5%	Exacerbation requiring hospitalisation	de Vries et al., 2010(69)
Suzuki et al., 2017**(140)**	2%	Severe exacerbations	Brazilian statistics
van Nooten et al., 2013**(141)**	2.48%	Severe exacerbations	Watson et al., 2007(67)
Whittington et al., 2017**(88)**	2.48%	Severe exacerbations leading to hospitalisation	Watson et al., 2007(67)

Three previous HTA models for asthma biologics used varying probabilities of death due to asthma exacerbations dependent on age (60, 64, 65), with two specifically reporting the values used (Table 139)(64, 65, 81). The other assessment did not report the values used but reported use of odds ratios from a study by Roberts and colleagues(68) which were applied to UK life tables (60).

Table 139. Input Values Used to Model Death due to Exacerbation in the Mepolizumab Submission to NICE (64, 81)

Age group	p (%) applied to the rate of exacerbations requiring a hospitalisation	p (%) applied to the rate of exacerbations requiring ED visit	p (%) applied to the rate of exacerbations requiring OCS

Manufacturer submitted base case			
<12	0.10%	0.07%	0.01%
12–16	0.32%	0.23%	0.05%
17–44	0.38%	0.28%	0.06%
≥45	2.48%	1.79%	0.38%
Revised base case / accepted			
12–16	0.176%	0.23%	0.05%
17–44	0.295%	0.28%	0.06%
45–54	0.923%	1.79%	0.38%
55–64	1.523%	1.79%	0.38%
≥65	4.545%	1.79%	0.38%

Discussions in NICE assessments of previous biologics on the appropriate source to use are summarised in Table 140 below.

Table 140. Decision-making Process for Source of Asthma-related Mortality in Previous Submissions of Monoclonal Antibodies to NICE

Submission	Approaches used for estimation of asthma-related mortality
Mepolizumab (TA431)(64, 81)	Manufacturer's submission: Conducted systematic review and found two studies relevant and informative for UK: Watson et al. 2007(67) and Roberts et al. 2013 (68). Watson was deemed preferable to Roberts, "since Roberts required absolute deaths to be estimated that may differ from the observed data, the definition of severe asthma was not specifically defined and the long study period over which care is likely to have changed." Base case: **Watson et al. 2007 + NRAD** • Watson et al. provide mortality data for asthma-related hospitalisation. Those were used for clinically significant exacerbations leading to hospitalisations in the model of mepolizumab, for the age bands provided by Watson et al. • To derive mortality data for other types of clinically significant exacerbations in the model (i.e., requiring use of systemic CS or requiring an ED visit), the NRAD was used as a source of data on asthma death by location (in community / on the way to hospital / in hospital). The manufacturer assumed that all the mortality data in NRAD applied to their population of interest (i.e., regardless of asthma severity, eosinophilic status, etc) and assumed that the proportion of asthma deaths occurring in the community could be applied for exacerbations requiring systemic CS and the proportion of asthma deaths occurring on the way to the hospital could be applied for exacerbations requiring an ED visit. Scenarios: • Watson 2007 alone (therefore, asthma-related death is only considered for exacerbations requiring hospitalisation) • Midpoint between estimates from Watson 2007 and from de Vries 2010 (69), plus 15% to represent a very severe uncontrolled asthma population (approach taken in omalizumab submission TA278) • Midpoint between estimates from Watson 2007 and from de Vries 2010 • Roberts 2013 Main ERG/Assessment Group/NICE critiques and/or recommendations: • Watson et al. used age categories but used a constant rate for those aged ≥ 45 years. The ERG deemed inappropriate to use a constant mortality rate for patients aged ≥ 45 years, as evidenced by the data reported by Roberts et al. The ERG recommended to use the stratification as in Roberts et al. (45–54, 55–64 and ≥ 65 years), which account for the increase in mortality rates after the age of 45 years whereas those from Watson et al. do not.

	• Should any of the deaths in Watson et al. be assignable to the 'hospital, pre-hospital arrest' category (in NRAD), then the number of deaths due to asthma exacerbations would be overestimated. Manufacturer's additional analyses in response to critiques/comments: The company undertook a retrospective cohort analysis using the same database as that used to inform Watson et al. (the CHKS database) and performed two exploratory analyses using Watson et al. + Roberts et al. with two different approaches: • Applying the rate ratios derived from comparing the rate for the 35-44 age band with the other age bands as reported by Roberts et al. to the mortality rate reported by Watson et al. for the 17-44 age band (option 1) • Assuming the same number of exacerbations across the three age bands and fitting the total deaths reported by Watson et al. in a way that the relative RRs of the different age bands were similar to those reported by Roberts et al. (option 2). ➔ The ERG preferred option 2.
Reslizumab (TA479)(60, 142)	Manufacturer's submission: Used **Roberts et al. 2013.** Also considered Watson et al. 2007 but chose Roberts chosen "as it stratifies patients into narrower age bands than those in Watson et al.". Applied the odds ratios from Roberts et al. to the national UK life tables. Main ERG/Assessment Group/NICE critiques and/or recommendations: This was not criticised by the ERG nor by the NICE committee.
Omalizumab (TA278)(61, 143)	Manufacturer's submission: Conducted a systematic review and identified 5 studies conducted in the UK: • Watson et al. 2007(67) • Gupta et al. 2004(144) and Wildman et al. 2009(145) but reported mortality following admission to the ICU. • Kearney et al. 1998,(146) Seddon and Heaf 1990,(147) and Gupta et al. 2004 but reported mortality in patients who required mechanical ventilation. Base case: **Watson et al. 2007** as manufacturer concluded that it "provided the only UK-specific data on the mortality risk from exacerbations resulting in non-ICU related hospitalisations". Scenarios: • Watson et al. 2007, but applying the mortality estimate not stratified by age • Lowhagen et al. 1997(134) (this was the source used in the original submission [TA201], a Swedish observational study on data collected between 1988 and 1990) • Gupta et al. 2004 (see above) Main ERG/Assessment Group/NICE critiques and/or recommendations: • Watson et al. provide mortality risk following hospitalisation for acute severe asthma, while in the model it is applied to all clinically significant severe (CSS) exacerbations: this may have resulted in an overestimation of asthma deaths because only about 20% of CSS exacerbations in the clinical trial from which the exacerbation data originated (INNOVATE) involved hospital admissions. • Manufacturer did not apply the age-dependent rates from Watson et al. but instead used the value for ≥ 45 years for the whole population (mean starting age of cohort was 43 years old). Assessment Group's model: The Assessment Group also conducted a systematic review and identified two potential sources: de Vries et al. 2010 and Watson et al. 2007. Elected to use de Vries et al. since the GPRD study reported data stratified by severity and included deaths in the community. Base case: **de Vries et al. 2010** (used the value estimated for Step 5 in BTS/SIGN guidelines) • Mortality risk applied to all patients in the model.

- Not stratified by age.

Scenarios:

- For patients < 18 years of age only: Watson et al. 2007 (using ICD10 code J46, i.e., for acute severe asthma)
- For all patients: Watson et al. 2007 (ibid)

Comparing the two sources, the Assessment Group identified that the risk of mortality was similar for patients aged 12-44 years but for patients ≥ 45 years, the risk of asthma-related death reported in de Vries was about one fifth of the risk reported by Watson. However, this was considered consistent with Watson since approximately 20% of the clinical significant severe exacerbations in INNOVATE involved hospitalisation.

Additional analyses requested from Assessment Group by the Appraisal Committee at the 1st Appraisal Committee meeting:

New analyses conducted for three particularly severe subpopulations.

Base case: **Watson et al. 2007**

Scenarios:

- **Watson et al. 2007 + 15% (to represent the most severe asthma population)**
- **de Vries et al. 2010 + 15% (ibid)**

Additional analyses submitted by the manufacturer after the 2nd Appraisal Committee meeting:

Midway between the estimates from Watson et al. and de Vries et al. + 15%.

This approach was the one used for the determination of what was the eventual "most plausible ICER" in the omalizumab appraisal.

The Appraisal Committee concluded that the 15% increase in mortality risk was an appropriate approximation of the mortality risk in very severe allergic asthma.

The Appraisal Committee also concluded that a more realistic mortality rate likely lays between the midpoint and the estimate from de Vries et al.

The Appraisal Committee concluded that both the Watson et al. and the de Vries et al. studies had limitations, that considerable uncertainty remained about the mortality associated with severe persistent asthma, and that neither may reflect mortality among the subgroups of people with very severe persistent asthma.

Appendix U. Treatment-dependent Utility Values Used in Earlier Evaluations

Previous HTA submissions and economic evaluations have considered the following as predictors of HRQoL:

- Treatment(61, 63, 64, 85, 133, 141, 148, 149)
- Response to treatment(61, 64, 85, 88, 133, 141, 148)
- Degree of asthma control(60, 150)
- Asthma exacerbations(60, 61, 63, 64, 85-87, 133, 138, 141, 148-154)
- Asthma symptoms(138)
- Lung function(89)
- OCS-related AEs(61, 63, 64)

Table A1. Utility Values by Treatment used in Previous Economic Evaluations

Study	Population	Methodology	Source	Add-on Treatment	Utility value			Incremental Utility Add-on versus SoC	
					SoC	Add-on Treatment: All patients	Add-on Treatment: Responders	All patients	Responders
NICE, 2016, TA431(64)	Adults with severe eosinophilic asthma: ITT population	SGRQ mapped to EQ-5D	MENSA trial	Mepolizumab	0.738	0.796	0.806	0.058	0.068
		EQ-5D	DREAM Phase IIb		0.794	0.802	0.824	0.008	0.03
	GSK proposed population excluding mOCS users with < 4 exacerbations	SGRQ mapped to EQ-5D	MENSA trial		0.682	0.793	0.805	0.111	0.123
		EQ-5D	DREAM Phase IIb		0.797	0.829	0.834	0.032	0.037
	GSK proposed population: blood eosinophil count of 150 cells/µl at initiation of treatment and 4 or more exacerbations in the previous year or were dependent on systemic corticosteroids	SGRQ mapped to EQ-5D	MENSA trial		0.708	0.777	0.795	0.069	0.087
		EQ-5D	DREAM Phase IIb		0.785	0.827	0.837	0.042	0.052
Institute for Clinical and Economic Review, 2015(63)	Adults with severe, uncontrolled asthma and evidence of eosinophilic inflammation, treated with high-dose ICS therapy and at least one additional controller medication	SGRQ mapped to EQ-5D	MENSA trial	Mepolizumab	0.77	0.828		0.058	
Whittington et al., 2017(88)	Adults with severe uncontrolled asthma and evidence of eosinophilic inflammation	SGRQ mapped to EQ-5D	MENSA trial	Mepolizumab	0.77	0.828		0.058	
Norman et al., 2013(61)	Patients uncontrolled at Step 4, and in the process of moving up to Step 5 (maintenance OCS), and patients controlled at Step 5	EQ-5D	EXALT trial	Omalizumab	0.719		0.767		0.048

	whose asthma would be uncontrolled if they were on Step 4 therapy								
	As above, restricted to patients experiencing a hospitalisation in the year prior to enrolment				0.631		0.761		0.13
	Restricted to patients receiving maintenance OCS at randomisation				0.686		0.791		0.105
Brown et al., 2007(133)	Patients with severe persistent allergic asthma despite high-dose ICS plus LABA	Mini-AQLQ mapped to EQ-5D	ETOPA trial	Omalizumab	0.65		0.82		0.17
Campbell et al., 2010(85)	Adults with moderate-to-severe persistent asthma, a positive skin test or in vitro reactivity to a perennial aeroallergen, and symptoms inadequately controlled with ICS	AQLQ mapped to EQ-5D	INNOVATE	Omalizumab	0.669	0.732	0.779	0.063	0.11
Dewilde et al., 2006(148)	Adult patients suffering from severe persistent, IgE-mediated allergic asthma who are uncontrolled despite GINA Step 4 therapy	AQLQ mapped to EQ-5D	INNOVATE	Omalizumab	0.669		0.779		0.11
Suzuki et al., 2017(140)	Patients with uncontrolled severe allergic asthma in a Brazilian healthcare setting	AQLQ mapped to EQ-5D	eXpeRience Study	Omalizumab	0.608	0.81	0.821	0.202	0.213
van Nooten et al., 2013(141)	Adult patients (≥12 years) with uncontrolled allergic (IgE mediated) asthma despite treatment with high-dose ICS (>1000 mg beclomethasone) and a LABA	Reported to be EQ-5D; however assumptions are unclear	PERSIST Study	Omalizumab	0.611		0.763		0.152

Appendix V. Summary of study results dupilumab, children with type 2 inflammation

Outcome	Dupilumab (n=236)	Placebo (n=114)	AD (95% CI)	RD (95% CI)	p-value
Efficacy results					
Annualized rate of severe asthma exacerbations during 52-week treatment period (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with at least 1 severe asthma exacerbation event during the 52 week period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from BL at week 12 of ppFEV1, (±SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% patients with >=200mL improvement in FEV1 at week 12 (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from BL at week 24 of ACQ-7-IA, (±SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from BL at week 52 of PAQLQ-IA global score (+SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from BL at week 52 of PRQLQ global score (+SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD, Absolute difference; RD, Relative difference; BL, baseline; CI, Confidence Interval; NA, not available; ppFEV1, predicted prebronchodilator FEV1; RD. **Note:** #, p-value for AD; *, p-value for RD. Type 2 inflammation is defined as peripheral eosinophils (≥0.15 Giga/L) and/or elevated FeNO (≥20 ppb)

Appendix X. Efficacy and safety of dupilumab dosing Q4W

The q4w dosing is approved by the European Medicines Agency and the scientific background is described in the EPAR. The dosing of dupilumab in Denmark in children 6 to 11 years of age with asthma is illustrated in Table1. Evidence supporting the dosing is included.

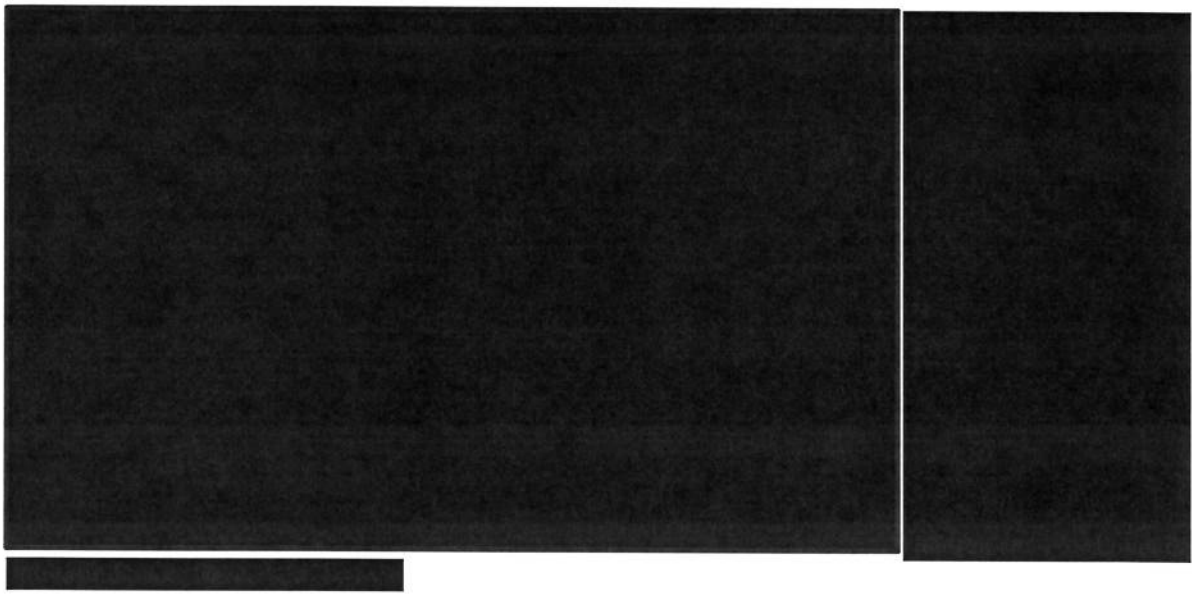
Table 1. Dose of dupilumab for subcutaneous administration in children 6 to 11 years of age with asthma

Body weight	Initial and subsequent dosing	Evidence supporting the dosing
15 to less than 30 kg	300 mg every four weeks (Q4W)	Pharmacokinetic analyses showing comparable simulated and observed steady-state dupilumab trough concentrations following dupilumab 300 mg q4w (simulated) and dupilumab 100 mg/200 mg q2w (actual) in pediatric patients (comparable dose-exposure) Additional supportive data is provided by the descriptive efficacy and safety of patients exposed to 300 mg q4w in the VOYAGE extension study (EXCURSION)
30 kg to less than 60 kg	300 mg every four weeks (Q4W)	Pharmacokinetic analyses showing comparable simulated and observed steady-state dupilumab trough concentrations following dupilumab 300 mg q4w (simulated) and dupilumab 100 mg/200 mg q2w (actual) in pediatric patients (comparable dose-exposure)
60 kg or more	200 mg every other week (Q2W)	Dosing investigated in QUEST (adults and adolescents)

Pharmakokinetic/exposure-response analyses

The VOYAGE study demonstrated efficacy and an acceptable safety profile of dupilumab 100 mg q2w and 200 mg q2w. Pharmacokinetic/exposure-response analyses based on data from VOYAGE demonstrate that simulation of a 300 mg q4w subcutaneous dose in children aged 6–11 years with body weight of ≥15–<30 kg and ≥30-<60 kg resulted in predicted steady-state through concentrations similar to the observed through concentrations of 200 mg q2w (≥30 kg) and 100 mg q2w (<30 kg) in children aged 6-11 years, respectively [redacted]

[redacted]



EXCURSION

Patients who completed the treatment period of the VOYAGE study could participate in the open label extension study (EXCURSION). As of the cut-off date of 25 June 2021, a total of 18 patients (8 in the placebo-dupilumab category and 10 in the dupilumab-dupilumab category) had been exposed to dupilumab 300 mg q4w for a cumulative exposure of 10.5 patient-years (mean [SD] duration of exposure: 213.9 [104.5] days). The safety profile was similar to that seen in VOYAGE.

There were no severe asthma exacerbations among the 18 patients that were exposed to 300 mg q4w dose regimen. Overall, the percentage predicted FEV1 remained stable for these individual patients over the timepoints evaluated after the switch to the dupilumab 300 mg q4w regimen in EXCURSION.

In an earlier datacut with 14 patients who were exposed to 300 mg q4w, 4 patients experienced TEAEs during their exposure to 300 mg q4w:1 in the placebo-dupilumab category (skin laceration) and 3 in the dupilumab-dupilumab category (headache and abdominal pain, injection site reaction, and scratch [right leg]). Of these 4 patients, 1 patient had a similar TEAE (injection site reaction) before switching to 300 mg q4w. None of the TEAEs reported during the 300 mg q4w exposure were serious or led to permanent treatment discontinuation.

No patients experienced SAE of asthma exacerbation and there was no treatment-emergent SAE in the patients exposed to the 300 mg q4w regimen. In addition, there were no TEAEs leading to treatment discontinuation reported in patients exposed to the 300 mg q4w regimen. Finally, no new ADRs were identified in the study.

During EXCURSION, changes in blood eosinophil mean or median from baseline were the same as the dupilumab group in the parent VOYAGE study. As to clinical chemistry, dupilumab treatment did not result in changes in electrolytes or metabolic parameters in either of the studies. Moreover, Dupilumab treatment did not result in changes in liver or renal function tests over the course of both studies (2).

QUEST

The dosing for the population ≥ 60 kg is supported by the QUEST study in adults/adolescents. When comparing data from QUEST and VOYAGE dupilumab reduced exacerbations in both the adult/adolescent and pediatric (aged 6 to < 12 years) populations with the type 2 inflammatory asthma phenotype. The magnitude of effect was similar across both populations. In the adult/adolescent study, the exacerbation reduction was 54.2% and 57.7% in the 200 mg q2w and 300 mg q2w groups, respectively and this was 59.3% for the pediatric population. Similar patterns were observed across populations selected by individual markers of type 2 inflammation including baseline eosinophils alone (eosinophils

≥ 0.15 Giga/L or eosinophils ≥ 0.3 Giga/L) or by baseline FeNO alone (≥20 ppb in children and ≥25 ppb in adolescents and adults).
Dupilumab improved lung function in both the adult/adolescent and pediatric (aged 6 to 12 years) populations with the type 2 inflammatory asthma phenotype across both studies. Despite the higher baseline mean percent predicted pre-BD FEV1 in the pediatric population, the magnitude of improvement was consistent across both populations. In the adult/adolescent study, the LS mean difference from placebo at Week 12 in percent predicted pre-BD FEV1 was 5.41% and 4.84% for the 200 mg q2w and 300 mg q2w groups, respectively and this was 5.21% for the pediatric population. Similar patterns were observed for patients identified by baseline eosinophils alone (eosinophils ≥0.15 Giga/L or eosinophils ≥0.3 Giga/L) or by baseline FeNO alone (≥20 ppb in children and ≥25 ppb in adolescents and adults) (2).

Conclusion

A weight-based dosing for pediatric patients with asthma age 6 to < 12 years was suggested as already existent for other indications. Efficacy results related to the diverse dose regimes of the Phase 3 studies were consistent for all efficacy populations. Efficacy and safety results do not give rise to any objections against this dose regimen which is already authorized for AD patients with a body weight of 15 ≤ 60 kg following a split loading dose of 300 mg each on Day 1 and 15. The analysis on efficacy results across the adult/adolescent and pediatric populations delivered similar results.
The 300 mg q4w dose is supported by PK and PK/PD analyses and simulations in children 6 to <12 years of age and in adults and adolescents with asthma, the efficacy and safety data observed in Studies VOYAGE and EXCURSION including descriptive efficacy and safety data of 300 mg q4w in Study EXCURSION, as well as supportive safety and PK data from children 6 to <12 years of age with AD from the Phase 3 study R688-AD-1652.
Overall, the dupilumab 300 mg q4w dose is anticipated to provide a benefit-risk profile similar to the 100 mg/200 mg q2w doses across weight groups.

References

(1) Data on file
(2) Dupixent, European Public Assessment Report, April 2022, Accessed via https://www.ema.europa.eu/en/documents/variation-report/dupixent-h-c-004390-x-0045-g-epar-assessment-report_en.pdf

Appendix B Main characteristics of included studies

Table 88 Study characteristics for Liberty Asthma VOYAGE

Trial name: Liberty Asthma VOYAGE	NCT number: 02948959
Objective	*To evaluate the efficacy of dupilumab in children 6 to <12 years of age with uncontrolled persistent asthma*
Publications – title, author, journal, year	*Dupilumab in Children with Uncontrolled Moderate-to-Severe Asthma, L.B. Bacharier, J.F. Maspero, C.H. Katelaris, A.G. Fiocchi, R. Gagnon, I. de Mir, N. Jain, L.D. Sher, X. Mao, D. Liu, Y. Zhang, A.H. Khan, U. Kapoor, F.A. Khokhar, P.J. Rowe, Y. Deniz, M. Ruddy, E. Laws, N. Patel, D.M. Weinreich, G.D. Yancopoulos, N. Amin, L.P. Mannent, D.J. Lederer, and M. Hardin, N. Eng. Jour. Medicine, 2021*
Study type and design	*A phase 3 multinational, multicentre, randomized, double-blind, placebo-controlled clinical trial designed to demonstrate the efficacy and safety of dupilumab administered for up to 52 weeks in addition to standard of care maintenance therapy in children 6 to <12 years of age with uncontrolled moderate-to-severe asthma*
Sample size (n)	*408*

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Trial name: Liberty Asthma VOYAGE	NCT number: 02948959

Main inclusion and exclusion criteria

Inclusion criteria :

Children 6 to <12 years of age, with a physician diagnosis of persistent asthma for ≥12 months prior to Screening, based on clinical history and examination, pulmonary function parameters according to Global initiative for asthma (GINA) 2015 Guidelines and the following criteria:

- *Existing background therapy of medium-dose inhaled corticosteroids (ICS) with second controller medication (ie, long-acting β2 agonist [LABA], leukotriene receptor antagonist [LTRA], long acting muscarinic antagonist [LAMA], or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller, for at least 3 months with a stable dose ≥1 month prior to Screening Visit 1.*
- *Pre-bronchodilator forced expiratory volume in 1 second (FEV1) ≤95% of predicted normal or pre bronchodilator FEV1/forced vital capacity (FVC) ratio <0.85 at Screening and Baseline Visits.*
- *Reversibility of at least 10% in FEV1 after the administration of 200 to 400 mcg (2 to 4 puff inhalations with metered-dose inhaler [MDI]) of albuterol/salbutamol or 45 to 90 mcg (2 to 4 puffs with MDI) of levalbuterol/levosalbutamol reliever medication before randomization (up to 3 opportunities during the same visit are allowed with a maximum of 12 puffs of reliever medication if tolerated by the patient).*
- *Must have experienced, within 1 year prior to Screening Visit 1, any of the following events:*
  - *Treatment with a systemic corticosteroid (SCS, oral or parenteral), as prescribed by a healthcare professional for worsening asthma at least once or,*
  - *Hospitalization or emergency room visit for worsening asthma.*
- *Evidence of uncontrolled asthma, with at least one of the following criteria during the 4 (±1) weeks Screening Period:*
  - *Asthma Control Questionnaire-Interviewer Administered (ACQ-IA) ACQ-5 score ≥1.5 on at least one day of the Screening Period.*
  - *Use of reliever medication (ie, albuterol/salbutamol or levalbuterol/levosalbutamol), other than as a preventive for exercise induced bronchospasm, on 3 or more days per week, in at least one week during the Screening Period.*
  - *Sleep awakening due to asthma symptoms requiring use of reliever medication at least once during the Screening Period.*
  - *Asthma symptoms 3 or more days per week in at least one week during the Screening Period*

Exclusion criteria:

- *Patients <6 or ≥12 years of age.*
- *Patients with <16 kg bodyweight.*
- *Any other chronic lung disease (cystic fibrosis, bronchopulmonary dysplasia, etc.), which may impair lung function.*
- *A subject with any history of life threatening asthma (ie, extreme exacerbation that requires intubation).*
- *Co-morbid disease that might interfere with the evaluation of investigational medicinal product (IMP)*

Trial name: Liberty Asthma VOYAGE	NCT number: 02948959
Intervention	The intervention was dupilumab and dosage was stratified by weight. Patients >30kg received 200 mg doses, while patients ≤30kg received 100 mg doses. Patients and investigators were blinded to the treatment, but not to the dose, meaning they were aware of whether they received/administered 200/100 mg. Out of 408 patients, 273 were allocated to the dupilumab arm.
Comparator(s)	*The comparator in the study was placebo and* dosage was stratified by weight. Patients >30kg received 200 mg doses, while patients ≤30kg received 100 mg doses. *Out of 408 patients, 135 was allocated to the placebo arm.*
Follow-up time	*Median follow-up duration was 365 days*
Is the study used in the health economic model?	*Yes*

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Trial name: Liberty Asthma VOYAGE	NCT number: 02948959

Primary, secondary and exploratory endpoints

Primary Outcome Measures :

1. *Annualized rate of severe exacerbation events during the placebo-controlled treatment period [Time Frame: Baseline, Week 52]*

Secondary Outcome Measures :

1. *Change from baseline in pre-bronchodilator % predicted forced expiratory volume in 1 second (FEV1) [Time Frame: Baseline, Week 12]*
2. *Change from baseline in pre-bronchodilator % predicted FEV1 [Time Frame: Baseline, Weeks 2, 4, 8, 24, 36, 52]*
3. *Time to first severe exacerbation event [Time Frame: Up to 52 weeks]*
4. *Time to first loss of asthma control event [Time Frame: Up to 52 weeks]*
5. *Change from baseline in other lung function measurements: absolute and relative FEV1 [Time Frame: Baseline, Weeks 2, 4, 8, 12, 24, 36, 52]*
6. *Change from baseline in other lung function measurements: AM/PM peak expiratory flow (PEF) [Time Frame: Baseline, Weeks 2, 4, 8, 12, 24, 36, 52]*
7. *Change from baseline in other lung function measurements: Forced Vital Capacity [Time Frame: Baseline, Weeks 2, 4, 8, 12, 24, 36, 52]*
8. *Change from baseline in other lung function measurements: Forced expiratory flow (FEF) 25-75% [Time Frame: Baseline, Weeks 2, 4, 8, 12, 24, 36, 52]*
9. *Change from baseline in other lung function measurements: Post bronchodilator % predicted FEV1 [Time Frame: Baseline, Weeks 2, 4, 8, 12, 24, 36, 52]*
10. *The effect of dupilumab on healthcare resource utilization [Time Frame: Baseline, Week 52]*
11. *Change from baseline in morning asthma symptom score [Time Frame: Baseline, Weeks 2, 4, 8, 12, 24, 36, 52]*
12. *Change from baseline in evening asthma symptom score [Time Frame: Baseline, Weeks 2, 4, 8, 12, 24, 36, 52]*
13. *Number of nocturnal awakenings due to asthma symptoms requiring the use of reliever medication [Time Frame: Baseline, Weeks 2, 4, 8, 12, 24, 36, 52]*
14. *Number of rescue medication inhalations [Time Frame: Baseline, Week 2, 4, 8, 12, 24, 36, 52]*
15. *Assessment of Patient Reported Outcomes: Asthma control questionnaire [Time Frame: Baseline, Weeks 2, 4, 8,12, 24, 36, 52,]*
16. *Assessment of Patient Reported Outcomes: Pediatric Asthma quality of life questionnaire [Time Frame: Baseline, Weeks 12, 24, 36, 52, 64]*
17. *Assessment of IgG responses to vaccination during dupilumab treatment (may be analyzed as exploratory endpoint if insufficient power) [Time Frame: 2 blood draws per vaccine scheduled:1 prevaccination and 1 post-vaccination.]*
18. *Change from baseline in fractional exhaled nitric oxide (FeNO) prior to spirometry [Time Frame: Baseline, Week 12]*
19. *Adverse Events [Time Frame: Up to Week 64]*
20. *Anti-Drug Antibodies [Time Frame: Baseline, Weeks 12, 24, 52, 64]*
21. *Serum Dupilumab Concentrations [Time Frame: Baseline, Weeks 6, 12, 24, 52, 64]*

Trial name: Liberty Asthma VOYAGE	NCT number: 02948959
Method of analysis	*There were 2 primary efficacy populations:* *• Type 2 inflammatory asthma phenotype population defined as the randomized patients with baseline blood eosinophil count ≥0.15 Giga/L or baseline FeNO ≥20 ppb;* *• Baseline blood eosinophil count ≥0.3 Giga/L population defined as the randomized patients with baseline blood eosinophil count ≥0.3 Giga/L.* *The primary efficacy endpoint, annualized rate of severe exacerbation events, was analyzed using a negative binominal regression model. The analysis for the annualized severe exacerbation rate was performed in the primary efficacy populations (the population with the type 2 inflammatory asthma phenotype and the population with baseline blood eosinophil count ≥0.3 Giga/L) and in additional efficacy populations identified on the basis of type 2 inflammatory biomarkers including either baseline blood eosinophil count ≥0.15 Giga/L or baseline FeNO ≥20 ppb independently, as well as the ITT population.* *For secondary efficacy endpoints MMRM approach was taken.* *The safety analysis was conducted for the safety population, which consisted of all patients who actually received at least 1 dose or part of a dose.*
Subgroup analyses	• *The population with baseline blood eosinophil count ≥0.15 Giga/L defined as the randomized patients with baseline blood eosinophil count ≥0.15 Giga/L.* • *The population with baseline FeNO ≥20 ppb defined as the randomized patients with baseline FeNO ≥20 ppb.* • *The full intent-to-treat (ITT) population, defined as all randomized patients.*
Other relevant information	*No*

Table 89. Main study characteristics for omalizumab

Trial name: OMALIZUMAB	NCT number: NCT00079937
Objective	*To evaluate the efficacy of omalizumab in children 6 to <12 years of age with inadequately controlled allergic (IgE-mediated) asthma*
Publications – title, author, journal, year	• *B. Lanier, T. Bridges, M. Kulus, A. F. Taylor, I. Berhane and C. F. Vidaurre, Omalizumb for the treatment of exacerbations in children with inadequately controlled allergi (IgE-mediated) asthma, 2010, J Allergy Clin Immunol, doi: 10.1016/j.jaci.2009.09.021.* • *M. Kulus, J. Hebert, E. Garcia, A. Fowler Taylor, C. Fernandez Vidaurre, M. Blogg, Omalizumab in children with inadequately controlled severe allergic (IgE-mediated) asthma, 2009, Curr Med Res Opin, doi: 10.1185/03007991003771338*
Study type and design	*Randomized, double-blind, placebo-controlled, parallel group, phase 3 trial*
Sample size (n)	*628*

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Trial name: OMALIZUMAB	NCT number: NCT00079937

Main inclusion and exclusion criteria

Inclusion criteria:

- Parent or legal guardian was informed of the study procedures and medications and gave written informed consent.
- Outpatient males and females aged 6 to < 12 years on study entry, with body weight between 20 and 150 kg.
- Total serum IgE level ≥ 30 to ≤ 1300 IU.
- Diagnosis of allergic asthma ≥ 1 year duration, according to American Thoracic Society (ATS) criteria, and a screening history consistent with clinical features of moderate or severe persistent asthma according to National Heart Lung and Blood Institute (NHLBI) guidelines.
- Positive prick skin test to at least one perennial allergen, documented within the past 2 years or taken at Screening. A radioallergosorbent test (RAST) could have been performed for patients with a borderline skin prick test result after consultation with Novartis clinical personnel.
- Patients with ≥ 12% increase in forced expiratory volume in 1 second (FEV1) over starting value within 30 minutes of taking up to 4 puffs (4x100 µg) salbutamol (albuterol) or nebulized salbutamol up to 5 mg (or equivalent of alternative B2-agonist) documented within the past year, at screening, during the run-in period, or prior to randomization. Patients were not to take their long acting B2-agonist (LABA) medication within 12 hours of reversibility testing.
- Clinical features of moderate or severe persistent asthma (at least step 3) despite therapy at step 3 or 4 (at least medium dose inhaled corticosteroid (ICS) - fluticasone dry-powder inhaler (DPI) ≥ 200 mg/day or equivalent with or without other controller medications).
- Documented history of experiencing asthma exacerbations and demonstrated inadequate symptom control during the last 4 weeks of run-in despite receiving an equivalent dose of fluticasone DPI ≥ 200 mg/day total daily ex-valve dose.

Exclusion criteria:

- Patients who received systemic corticosteroids for reasons other than asthma, beta-adrenergic antagonists by any route, anticholinergics within 24 hours of Screening, methotrexate, gold salts, cyclosporin or troleandomycin, or had received desensitization therapy with less than 3 months of stable maintenance doses prior to Screening.
- Patients with a history of food or drug related severe anaphylactoid or anaphylactic reaction, a history of allergy to antibiotics, with aspirin or other non-steroidal anti-inflammatory drugs (NSAID)-related asthma (unless the NSAID could be avoided), with active lung disease or acute sinusitis/chest infection, elevated serum IgE levels for other reasons, presence/history of a clinically significant uncontrolled systemic disease, cancer, abnormal, electrocardiogram (ECG) in the previous month, or platelets ≤ 100 x 109/L or clinically significant laboratory abnormalities at Screening.

Intervention	*Omalizumab*
Comparator(s)	*Placebo*
Follow-up time	*52 weeks*

Trial name: OMALIZUMAB	NCT number: NCT00079937
Is the study used in the health economic model?	*Yes*

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Primary, secondary and exploratory endpoints

Primary

1. *Rate of Clinically Significant Asthma Exacerbations Per Patient in the 24-week Fixed-dose Steroid Treatment Period [Time Frame: Baseline to end of the fixed-dose steroid treatment period (Week 24)]*

   A clinically significant asthma exacerbation was defined as a worsening of asthma symptoms, as judged clinically by the investigator, requiring doubling of the baseline inhaled corticosteroid dose and/or treatment with systemic rescue corticosteroids for at least 3 days. The exacerbations rate per patient was derived using Poisson model adjusted by time at risk and the following covariates: country, exacerbation history, and dose schedule. A patient's person-days at risk was taken as the total amount of time (in days) he/she spent in the 24-week fixed-dose steroid treatment period.

2. *Percentage of Participants With at Least 1 Adverse Event [Time Frame: Baseline to end of the study (Week 68)]*

Secondary

3. *Change in Mean Nocturnal Asthma Symptom Score From Baseline to the End (Last 4 Weeks) of the 24-week Fixed-dose Steroid Treatment Period [Time Frame: Baseline to the end (last 4 weeks) of the 24-week fixed-dose steroid treatment period]*

   Nocturnal asthma symptom was measured daily on a scale of 0 to 4 in response to the question "How did you sleep last night?", with 0 as the best response and 4 as the worst response. The mean of the last 4 weeks of the 24-week fixed-dose steroid treatment period was calculated; for patients who discontinued prematurely, the mean of the last 28 days before discontinuation was calculated. A negative change in mean score indicated improvement.

4. *Rate of Clinically Significant Asthma Exacerbations Per Patient in the 52-week Treatment Period [Time Frame: Baseline to end of the treatment period (Week 52)]*

   A clinically significant asthma exacerbation was defined as a worsening of asthma symptoms, as judged clinically by the investigator, requiring doubling of the baseline inhaled corticosteroid dose and/or treatment with systemic rescue corticosteroids for at least 3 days. The exacerbations rate per patient was derived using Poisson model adjusted by time at risk and the following covariates: country, exacerbation history, and dose schedule. A patient's person-days at risk was taken as the total amount of time (in days) he/she spent in the 52-week treatment period.

5. *Change in Mean Daily Number of Puffs of Asthma Rescue Medication From Baseline to the End (Last 4 Weeks) of the 24-week Fixed-dose Steroid Treatment Period [Time Frame: Baseline to the end (last 4 weeks) of the 24-week fixed-dose steroid treatment period]*

   Patients were instructed to record the number of puffs of rescue medication they took twice daily in a diary. The mean daily number of puffs during the last 4 weeks of the 24-week fixed-dose steroid treatment period was calculated; for patients who discontinued prematurely, the mean of the last 28 days before discontinuation was calculated. A negative change in mean daily number of puffs indicated reduced use of rescue medication.

6. *Change in Pediatric Asthma Quality of Life Questionnaire (Standardized) [PAQLQ(S)] Scores From Baseline to the End of the 24-week Fixed-dose Steroid Treatment Period (Week 24) [Time Frame: Baseline to the end of the 24-week fixed-dose steroid*

Trial name: OMALIZUMAB	NCT number: NCT00079937
	treatment period (Week 24)] *PAQLQ measures functional problems that are most troublesome to children with asthma. PAQLQ has 23 questions in 3 domains (activity limitation=5, emotional function=8, symptoms=10). Patients responded to each question on a 7-point Likert scale. Overall PAQLQ score is mean of 23 questions; each domain score is mean of questions in that domain. Minimum possible value is 1 (maximum impairment); maximum possible value is 7 (no impairment). Positive change indicated improvement. The analysis included country, baseline PAQLQ value, and dosing schedule (2-weekly/4-weekly) as factors and covariates.*
Method of analysis	*Statistical differences between group baseline characteristics were tested using the F-test, chi-squared test and Fisher's exact test, as appropriate.* *Rate of clinically significant asthma exacerbations over 24 and 52 weeks were compared between treatment groups using a two-sided test at a=0.05 with a generalized Poisson regression model. The rate ratio (RR) of exacerbations between the treatment groups and 95% confidence interval (CI) were obtained.* *For patients who discontinued early, exacerbation data were imputed for clinically significant exacerbations over 24 and 52 weeks (one added to the total number for patients who discontinued prematurely, unless they had an exacerbation ≤7 days prior to discontinuation).* *The percentage change from baseline in ICS dose was compared using the van Elteren test: a non-parametric test that compares treatments in the presence of blocking (an extension of Wilcoxon's rank-sum test); percent change in ICS dose for patients who discontinued before the 28-week adjustable-steroid phase was imputed as zero. The numbers of patients rated as excellent or good according to the physician's GETE were compared using the Cochran Mantel Haenszel test.* *Assessment of safety was based on the frequency of all AEs. Statistical differences between the frequency of AEs reported in the omalizumab and placebo groups were calculated using Fisher's exact test.*
Subgroup analyses	*Children with inadequately controlled severe asthma, despite receiving high-dose ICS (≥500 mg · day^{-1} FP or equivalent) and a LABA, with or without other controller medications, Kulus et al. 2010 (16)*
Other relevant information	*No*

Table 90 Main study characteristics for mepolizumab

Trial name: MEPOLIZUMAB	NCT number: 02377427
Objective	*To evaluate the pharmacokinetics and pharmacodynamics, along with long-term safety of mepolizumab in children 6 to <12 years of age with severe eosinophilic asthma*
Publications – title, author, journal, year	• *Gupta A, Pouliquen I, Austin D, Price RG, Kempsford R, Steinfeld J, Bradford ES, Yancey SW. Subcutaneous mepolizumab in children aged 6 to 11 years with severe eosinophilic asthma. Pediatr Pulmonol. 2019 Dec;54(12):1957-1967. doi: 10.1002/ppul.24508. Epub 2019 Sep 9. PMID: 31502421; PMCID: PMC6972599.* • *Gupta A, Ikeda M, Geng B, Azmi J, Price RG, Bradford ES, Yancey SW, Steinfeld J. Long-term safety and pharmacodynamics of mepolizumab in children with severe asthma with an eosinophilic phenotype. J Allergy Clin Immunol. 2019 Nov;144(5):1336-1342.e7. doi: 10.1016/j.jaci.2019.08.005. Epub 2019 Aug 16. PMID: 31425781.*
Study type and design	*An open-label, non-randomized, multinational interventional study*
Sample size (n)	*36*

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Main inclusion and exclusion criteria	**Inclusion Criteria:** • Between 6 and 11 years of age inclusive, at the time of screening. • Diagnosis of severe asthma, defined by the regional asthma guidelines (i.e., National Institute of Health (NIH), Global Initiative for Asthma (GINA), etc.), for at least 12 months prior to Visit 1. If the participant is naïve to the study site, the participant/guardian must self-report a physician diagnosis of asthma and the investigator must confirm by review of medical history with the participant/guardian. • Eosinophilic airway inflammation that is related to asthma characterized as eosinophilic in nature as indicated by: elevated peripheral blood eosinophil count of >=300 cells per microliter (cells/µL) demonstrated in the past 12 months OR elevated peripheral blood eosinophil count of >=150/µL at visit 1. • A well-documented requirement for regular treatment with inhaled corticosteroid (>200 µg/day fluticasone propionate drug powder inhaler [DPI] or equivalent daily) in the 12 months prior to Visit 1 with or without maintenance oral corticosteroids (OCS). The ICS dose should represent medium or high dose in children aged 6-11 years of age [GINA, 2015]. • Current treatment with an additional controller medication for at least 3 months or a documented failure in the past 12 months of an additional controller medication for at least 3 successive months. [e.g., long-acting beta-2-agonist (LABA), leukotriene receptor antagonist (LTRA), or theophylline.] • Forced expiratory volume in one second (FEV1): Persistent airflow obstruction at either Visit 1 or Visit 2 (FEV1 performed prior to first dose of study medication) as indicated by: A pre-bronchodilator FEV1 <110% predicted (Quanjer, 2012) OR FEV1: Forced vital capacity (FVC) ratio <0.8. • Previously confirmed history of two or more exacerbations requiring treatment with systemic corticosteroids (CS) (intramuscular [IM], intravenous, or oral), in the 12 months prior to visit 1, despite the use of high-dose inhaled corticosteroids (ICS). For participants receiving maintenance CS, the CS treatment for the exacerbations must have been a two-fold increase or greater in the dose. • No changes in the dose or regimen of baseline ICS and/or additional controller medication during the run-in period. • Male or female: Females of childbearing potential must commit to consistent and correct use of an acceptable method of contraception for the duration of the trial and for 4 months after the last dose of investigational product. A urine pregnancy test is required of girls of childbearing potential. This test will be performed at the initial screening visit (visit 1) and will be performed at each scheduled study visit prior to the administration of investigational product, and during the early withdrawal and follow-up visits. • Parent(s)/guardian able to give written informed consent prior to participation in the study, which will include the ability to comply with the requirements and restrictions listed in the consent form. If applicable, the participant must be able and willing to give assent to take part in the study according to the local requirement. • For Part B: The subject has completed all study assessments up-to and including Visit 8 and received all 3 doses of investigational product (IP) in Part A • For Part B: The Principal Investigator (PI) has performed a benefit/risk assessment and this assessment supports continued therapy with mepolizumab. • The subject's parents (or guardian) have given consent and the subject has given assent for continued treatment **Exclusion Criteria:** • Participants with any history of life threatening asthma (e.g. requiring intubation), immunosuppressive medications intake or immunodeficiency disorder.

Trial name: MEPOLIZUMAB	NCT number: 02377427

- Participants with any medical condition or circumstance making the volunteer unsuitable for participation in the study.
- Significant abnormality of rate, interval, conduction or rhythm in the 12-lead electrocardiogram (ECG), determined by the investigator in conjunction with the age and gender of the child at Visit 1.
- Alanine aminotransferase (ALT), and bilirubin >2x upper limit of normal (ULN) (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at Visit 1.
- Positive Hepatitis B Surface Antigen or positive Hepatitis C antibody at Visit 1.
- Parent/guardian has a history of psychiatric disease, intellectual deficiency, substance abuse, or other condition (e.g. inability to read, comprehend and write) which will limit the validity of consent to participate in this study.
- Unwillingness or inability of the participant or parent/guardian to follow the procedures outlined in the protocol.
- Participant who is mentally or legally incapacitated.
- Children who are wards of the state or government.
- A participant will not be eligible for this study if he/she is an immediate family member of the participating investigator, sub-investigator, study coordinator, or employee of the participating investigator.
- Omalizumab: Participants who have received omalizumab within 130 days of Visit 1.
- Other Biologics: Participants who have received any biological (other than omalizumab) to treat inflammatory disease within 5 half-lives of visit 1.
- History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.
- Hypersensitivity: Participants with allergy/intolerance to a monoclonal antibody or biologic.
- The participant has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).

Intervention	The intervention was 40 mg of mepolizumab for children with a body weight <40kg or 100 mg for children with a body weight ≥40kg, via subcutaneous injections administered every 4 weeks for 12 weeks. Some patients received both dosages, as they went from <40kg to ≥40kg during the study.
Comparator(s)	*Single-arm study*
Follow-up time	*72 weeks*
Is the study used in the health economic model?	*Yes*

Primary, secondary and exploratory endpoints

Primary Outcome Measures :

1. Maximum Plasma Concentration (Cmax) of Mepolizumab for Part A [Time Frame: Pre-dose on Weeks 4 and 8; Weeks 9, 12, 16 and 20 post-dose]
2. Area Under Concentration Time Curve to Infinity (AUC [0-inf]) of Mepolizumab for Part A [Time Frame: Pre-dose on Weeks 4 and 8; Weeks 9, 12, 16 and 20 post-dose]
3. Terminal Phase Elimination Half-life (T1/2) of Mepolizumab During Treatment Period for Part A [Time Frame: Pre-dose on Weeks 4 and 8; Weeks 9, 12, 16 and 20 post-dose]
4. Plasma Apparent Clearance (CL/F) of Mepolizumab in Part A [Time Frame: Pre-dose on Weeks 4 and 8; Weeks 9, 12, 16 and 20 post-dose]
5. Ratio to Baseline in Absolute Blood Eosinophil Count at Week 12 for Part A [Time Frame: Baseline and Week 12]
6. Number of Participants With on Treatment Serious Adverse Events (SAEs) and Non-SAEs for Part B [Time Frame: From Week 20 and up to Week 72]
7. Number of Participants With Positive Anti-mepolizumab Binding Antibodies and Neutralizing Antibodies Response for Part B [Time Frame: From Week 20 and up to Week 80]
8. Change From Baseline in Sitting Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) for Part B [Time Frame: Baseline and Weeks 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 80]
9. Change From Baseline in Sitting Pulse Rate for Part B [Time Frame: Baseline and Weeks 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 80]
10. Number of Participants With Any Time Change From Baseline Relative to Normal Range in Clinical Chemistry Parameters for Part B [Time Frame: Baseline, from Week 20 and up to Week 72]
11. Number of Participants With Any Time Change From Baseline Relative to Normal Range in Hematology Parameters for Part B [Time Frame: Baseline, from Week 20 and up to Week 80]
12. Number of Participants With Abnormal Findings for Urinalysis Parameters in Part B [Time Frame: From Week 20 and up to Week 72]

Secondary Outcome Measures :

1. Body Weight-adjusted Apparent Clearance of Mepolizumab for Part A [Time Frame: Pre-dose on Weeks 4 and 8; Weeks 9, 12, 16 and 20 post-dose]
2. Change From Baseline in Asthma Control Questionnaire-7 (ACQ-7) at Week 12 in Part A [Time Frame: Baseline and Week 12]
3. Change From Baseline in Asthma Control Questionnaire-7 (ACQ-7) at Weeks 4,8,16 and 20 in Part A [Time Frame: Baseline and Weeks 4,8,16 and 20]
4. Change From Baseline in Childhood Asthma Control Test (C-ACT) at Week 12 for Part A [Time Frame: Baseline and Week 12]
5. Change From Baseline in C-ACT at Weeks 4,8,16 and 20 in Part A [Time Frame: Baseline and Weeks 4,8,16 and 20]
6. Number of Participants With on Treatment SAEs and Non-SAEs in Part A [Time Frame: Up to Week 20]

Trial name: MEPOLIZUMAB	NCT number: 02377427

7. Number of Participants With Any Time Change From Baseline Relative to Normal Range in Hematology Parameters in Part A [Time Frame: Baseline and up to Week 20]
8. Number of Participants With Any Time Change From Baseline Relative to Normal Range in Clinical Chemistry Parameters in Part A [Time Frame: Baseline and up to Week 20]
9. Number of Participants With Abnormal Findings for Urinalysis in Part A [Time Frame: Up to Week 20]
10. Number of Participants With Positive Anti-mepolizumab Binding Antibodies and Neutralizing Antibodies Response in Part A [Time Frame: Baseline and Weeks 16 and 20]
11. Change From Baseline in Sitting SBP and DBP in Part A [Time Frame: Baseline and Weeks 4, 8, 9, 12, 16 and 20]
12. Change From Baseline in Sitting Pulse Rate in Part A [Time Frame: Baseline and Weeks 4, 8, 9, 12, 16 and 20]
13. Ratio to Baseline in Absolute Blood Eosinophil Count at Weeks 32, 44, 56, 68, 72 and 80 for Part B [Time Frame: Baseline and Weeks 32, 44, 56, 68, 72 and 80]

Method of analysis	Part A; Mepolizumab plasma PK concentrations were analyzed by nonlinear mixed-effect modeling methods (SAS Institute Inc, Cary, NC). A two-compartment model with first-order absorption and elimination was used with PK distribution parameters and bioavailability fixed to previously estimated adult values. Bodyweight was incorporated into the model using physiological allometry with allometric exponents for clearance and volumes estimated. Final model appropriateness was assessed using goodness of fit plots, simulations, and statistical tests. The ratio of blood eosinophil count at week 12 to baseline was summarized descriptively, and the ratio at each visit to baseline presented graphically. Bodyweight-adjusted apparent clearance point estimates with 90% CIs in children 6 to 11 years were presented alongside the historical estimated adult value of 0.29 L/day (unpublished data) with a proposed 80% to 125% interval around this estimate of 0.23 to 0.36 L/day. An exploratory population PK analysis using the most recent mepolizumab population PK model with minimal estimation (absolute bioavailability, allometric exponents, and residual error) was conducted using NONMEM software (version 7.2; ICON Development Solutions, Ellicott City, MD). Part B: All statistical analyses were performed by using the safety population (all children who received >1 dose of mepolizumab within part B). Endpoints were summarized by using appropriate descriptive statistics (mean/geometric mean, median, SD, and range). AEs were summarized by using the Medical Dictionary for Regulatory Activities Primary System Organ Class and Preferred Terms. Annualized exacerbation rates were determined by using a negative binomial generalize linear model with logarithm of time as an offset variable, from which estimates rates per year and 95% CIs were calculated. For blood eosinophil counts, the ratio to baseline was summarized by visit; if a result of zero was recorded, a small value (half the minimum nonzero result) was imputed before log-transformation. For blood eosinophil counts and asthma control questionnaire scores, baseline was defined as the value recorded before the first mepolizumab treatment in part A (overall study week 0). All statistical analyses were performed with SAS software (version 9.4; SAS Institute, Cary, NC).
Subgroup analyses	children with severe asthma with an eosinophilic phenotype
Other relevant information	No

Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Liberty Asthma VOYAGE vs. IA05 (Kulus et al., 2010(16)) (severe allergic IgE asthma subgroup)

Table 91. Baseline characteristics of patients included in Liberty Asthma VOYAGE and IA05 for the comparative analysis of efficacy and safety

Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety				
	Liberty Asthma VOYAGE (Severe allergic subgroup)		IA05 (Kulus et al., 2010) (mITT)(16)	
	Placebo (n=63)	Dupilumab (n=115)	Placebo (n = 76)	Omalizumab (n =159)
Mean age (mean (SD))	[redacted]	[redacted]	8.6 (1.7)	9.1 (1.7)
Gender (% female)	[redacted]	[redacted]	31.6%	35.8%
Race (% white)	[redacted]	[redacted]	63.2%	57.9%
Mean weight (kg (SD))	[redacted]	[redacted]	NA	NA
High ICS dose level at baseline (%)	[redacted]	[redacted]	NA	NA
Mean time since first diagnosis of asthma (years (SD))	[redacted]	[redacted]	NA	NA
Number of severe asthma exacerbation experienced in the past year	[redacted]	[redacted]	NA	NA
Mean FEV1% predicted	[redacted]	[redacted]	82.6 (19.5)	81.8 (17.5)
Mean FEV_1 reversibility (% (SD))	[redacted]	[redacted]	25.1% (14.8)	29.4 (19.9)
Blood Eosinophil (cells/µL (SD))	[redacted]	[redacted]	NA	NA
Mean FeNO (ppb (SD))	[redacted]	[redacted]	NA	NA
Mean total IgE (IU/mL (SD))	[redacted]	[redacted]	414.0 (305.6)	452.4 (328.3)
Baseline Global PAQLQ-IA score	[redacted]	[redacted]	NA	NA

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Baseline Global PRQLQ-IA score	[redacted]	[redacted]	NA	NA
Ongoing atopic medical conditions [n (%)]	62 (98.4%)	115 (100%)	NA	NA
Ongoing atopic dermatitis , *[n (%)]*	19 (30.2%)	45 (39.1%)	NA	NA
Ongoing allergic conjunctivitis *[n (%)]*	13 (20.6%)	26 (22.6%)	NA	NA
Ongoing allergic rhinitis , *[n (%)]*	51 (81.0%)	96 (83.5%)	NA	NA
Ongoing eosinophilic esophagitis , *[n (%)]*	0	1 (0.9%)	NA	NA
Ongoing food allergy , *[n (%)]*	8 (12.7%)	22 (19.1%)	NA	NA
Ongoing hives *[n (%)]*	3 (4.8%)	13 (11.3%)	NA	NA

Liberty Asthma VOYAGE vs. Mepolizumab (Severe eosinophilic asthma)

Table 92. Baseline characteristics of patients included in Liberty Asthma VOYAGE and mepolizumab-trial (18) for the comparative analysis of efficacy and safety

Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety				
	Liberty Asthma VOYAGE (Severe eosinophilic subgroup)		**Mepolizumab (18)**	
	Placebo (n=130)	Dupilumab (n=254)	Mepolizumab 40mg (n=26)	Mepolizumab 100mg (n=10)
Mean age (mean (SD))	[redacted]	[redacted]	8.0 (1.8)	10.0 (1.3)
Gender (% female)	[redacted]	[redacted]	23%	50%
Race (% white)	[redacted]	[redacted]	NA	NA
Mean weight (kg (SD))	[redacted]	[redacted]	27.4 (4.7)	49.5 (6.3)
High ICS dose level at baseline (%)	[redacted]	[redacted]	NA	NA
Mean time since first diagnosis of asthma (years (SD))	[redacted]	[redacted]	NA	NA

Number of severe asthma exacerbation experienced in the past year	[redacted]	[redacted]	NA	NA
Mean FEV1% predicted	[redacted]	[redacted]	89 (16.9)	92 (6.9)
Mean FEV_1 reversibility (% (SD))	[redacted]	[redacted]	NA	NA
Blood Eosinophil (cells/µL (SD))	[redacted]	[redacted]	386 (0.75*)	331 (0.91*)
Mean FeNO (ppb (SD))	[redacted]	[redacted]	NA	NA
Mean total IgE (IU/mL (SD))	[redacted]	[redacted]	336 (1.48*)	379 (1.09*)
Baseline Global PAQLQ-IA score	[redacted]	[redacted]	NA	NA
Baseline Global PRQLQ-IA score	[redacted]	[redacted]	NA	NA
Ongoing atopic dermatitis [n (%)]	[redacted]	[redacted]	NA	NA
Ongoing allergic conjunctivitis [n (%)]	[redacted]	[redacted]	NA	NA
Ongoing allergic rhinitis, [n (%)]	[redacted]	[redacted]	NA	NA

Note: *, SD logs

Liberty Asthma VOYAGE (Severe asthma with elevated FeNO)

Table 93. Baseline characteristics of patients in Liberty Asthma VOYAGE, severe asthma with elevated FeNO expression subgroup

Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety		
	Liberty Asthma VOYAGE (Severe asthma with elevated FeNO subgroup)	
	Placebo (n=130)	**Dupilumab (n=254)**
Mean age (mean (SD))	[redacted]	[redacted]
Gender (% female)	[redacted]	[redacted]
Race (% white)	[redacted]	[redacted]

Mean weight (kg (SD))	[redacted]	[redacted]
High ICS dose level at baseline (%)	[redacted]	[redacted]
Mean time since first diagnosis of asthma (years (SD))	[redacted]	[redacted]
Number of severe asthma exacerbation experienced in the past year	[redacted]	[redacted]
Mean FEV1% predicted	[redacted]	[redacted]
Mean FEV_1 reversibility (% (SD))	[redacted]	[redacted]
Blood Eosinophil (cells/µL (SD))	[redacted]	[redacted]
Mean FeNO (ppb (SD))	[redacted]	[redacted]
Mean total IgE (IU/mL (SD))	[redacted]	[redacted]
Baseline Global PAQLQ-IA score	[redacted]	[redacted]
Baseline Global PRQLQ-IA score	[redacted]	[redacted]
Ongoing atopic dermatitis [n (%)]	[redacted]	[redacted]
Ongoing allergic conjunctivitis [n (%)]	[redacted]	[redacted]
Ongoing allergic rhinitis, [n (%)]	[redacted]	[redacted]

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Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
Severe asthma exacerbation	The frequency of severe asthma exacerbations.	Rate of asthma exacerbation has been used in prior DMC submission for asthma and for treatment guideline protocol (22, 23)	Used in prior DMC submission for asthma and for treatment guideline protocol (22, 23)
Lung function	% patients with >=200mL improvement in FEV1 at week 12 (95% CI)		The minimal clinically important difference for % patients with >=200mL improvement in FEV1 is 15% (19, 50)
FEV_1	FEV1 is the volume of air that can be forcibly expired in one second after a full inspiration.	Used in prior DMC submission for asthma and for treatment guideline protocol (22, 23)	The minimal clinically important difference for FEV_1 is 12% for children (19, 50)
ACQ-7-IA	ACQ is a patient-reported tool to assess asthma control in patient ≥ 6 years of age. It comprises the following seven questions, of which the mean of the results is the overall score (0 = well-controlled asthma and 6 = extremely poorly controlled asthma)	The Asthma Control Questionnaire (ACQ) has been shown to be a valid, reliable instrument that allows accurate and reproducible assessment of asthma control that compares favorably with other commonly used instruments (101). ACQ is used prior in DMC submissions for asthma and for treatment guideline protocol (50)	The minimal clinically important difference for ACQ is 0.5 (19, 50)
Pediatric Asthma Quality of Life Questionnaire (PAQLQ(S))	Pediatric Asthma Quality of Life Questionnaire	PAQLQ is a validated tool, which was developed to measure the problems that children with asthma experience in their day-to-day lives (102)	The Pediatric Asthma Quality of Life Questionnaire (PAQLQ) is one of the most widely used instruments for measuring health-related QoL in children with asthma. The standardized version of PAQLQ contains 23 questions in three domains, i.e., activity limitation, symptoms and emotional function .

Outcome measure	Definition	Validity	Clinical relevance
Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ)	Paediatric Rhinoconjunctivitis Quality of Life Questionnaire	(103)	The PRQLQ has 23 items in five domains (nose symptoms, eye symptoms, practical problems, other symptoms, and activities)
AEs	Adverse events can include any unfavourableClick or tap here to enter text. and/or unintended signs, abnormal laboratory tests, imaging analysis or other findings associated with the treatment. Adverse events may be expected or unexpected.	AEs as outcome measure are used in most studies evaluation safety of a the treatment of interest.	To investigate the safety profile of dupilumab compared to other comparators in the treatment of asthma with different characteristics.
SAE	Any untoward medical occurrence that at any dose. Results in death. Is life-threatening. Requires inpatient hospitalization or causes prolongation of existing hospitalization.	Used in prior DMC submission for asthma and for treatment guideline protocol (19, 50)	The minimal clinically important difference for treatment discontinuations due to AEs is 5%-point (19, 50)

Results per study

Severe allergic asthma

Table 94. Results of Liberty Asthma VOYAGE (NCT02948959) Severe Allergic Asthma

Results of Liberty Asthma VOYAGE (NCT02948959) for severe allergic asthma				
	Estimated absolute difference in effect	**Estimated relative difference in effect**	**Description of methods used for estimation**	**References**

Results of Liberty Asthma VOYAGE (NCT02948959) for severe allergic asthma

Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Annualized rate of severe asthma exacerbations during 52-week treatment period	Dupilumab	115	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	The annualized rate of severe exacerbation events was analyzed using a negative binominal regression model that includes the total number of events observed from randomization up to week 52 or last study contact date (whichever comes earlier) as the response variable, and includes treatment group, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, and number of severe exacerbation events within 1 year prior to the study as covariates, and log-transformed standardized observation duration as an offset variable.	(24)
	Placebo	63	[redacted]								
% experience no exacerbation during 52-week treatment periods, %	Dupilumab	115	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	All severe exacerbation events occurred during the 52-week treatment period are included, regardless of whether the patient is on-treatment or not	(24)
	Placebo	63	[redacted]								
Change from BL at week 12 of ppFEV1, (±SE)	Dupilumab	115	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Change from baseline in percentage of predicted FEV1 was analyzed using a mixed-effect model with repeated measures approach, including treatment, baseline weight, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment-by-visit interaction, baseline percentage of predicted FEV1 value, and baseline-by-visit interaction as covariates.	(24)
	Placebo	63	[redacted]								

Results of Liberty Asthma VOYAGE (NCT02948959) for severe allergic asthma													
% patients with >=200mL improvement in FEV1 at week 12 (95% CI)	Dupilumab	115	[redacted]									Patients with missing pre-bronchodilator FEV1 at W12 were considered as no improvement.	(24)
	Placebo	63	[redacted]										
Change from BL in ACQ-7-IA, (±SE)	Dupilumab	115	[redacted]									Derived from MMRM model with change from baseline in ACQ-7-IA up to Week 24 as the response variable, and treatment, age, weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline ACQ-7-IA and baseline-by-visit interaction as covariates.	(24)
	Placebo	63	[redacted]										
Change from BL at week 52 of PAQLQ-IA global score	Dupilumab	115	[redacted]									Derived from MMRM model with change from baseline in PRQLQ global score values up to Week 52 as the response variable, and treatment, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline PRQLQ global score and baseline-by-visit interaction as covariates.	(27)
	Placebo	63	[redacted]										
Change from BL at week 52 of PRQLQ	Dupilumab	115	[redacted]									Derived from MMRM model with change from baseline in PAQLQ(S)-IA global score values up to Week 52 as the response variable, and treatment, age, baseline weight group, region, baseline eosinophil level,	(27)
	Placebo	63	[redacted]										

Results of Liberty Asthma VOYAGE (NCT02948959) for severe allergic asthma											
global score (+SE)										baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline PAQLQ(S)-IA global score and baseline-by-visit interaction as covariates.	
AE, n (%)	Dupilumab	271	225 (83.0)	3.18%	(-4.96% - 11.31%)	NA	1.04	(0.94 - 1.15)	0.4565	The safety variables, including TEAEs, laboratory parameters, vital signs, ECG, and physical examinations will be summarized using descriptive statistics.	(27)
	Placebo	134	107 (79.9)								
SAE, n (%)	Dupilumab	271	13 (4.8)	0.32%	(-4.01% - 4.65%)	NA	1.07	(0.42 - 2.76)	0.8950		(27)
	Placebo	134	6 (4.5)								
AEs leading to discontinuation, n (%)	Dupilumab	271	5 (1.8)	0.35%	(-2.25% - 2.96%)	NA	1.24	(0.24 - 6.29)	0.8103		(27)
	Placebo	134	2 (1.5)								

Table 95. Results of IA05 (Kulus et al., 2010) (NCT00079937) for severe allergic asthma

Results of OMALIZUMAB (NCT00079937) for severe allergic asthma											
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	Omalizumab	159	0.42 (NA)	21.02	7.72 - 34.31	0.002	RR: 0.662	0.441, 0.995	0.047		(16)

Results of OMALIZUMAB (NCT00079937) for severe allergic asthma											
Clinically significant asthma exacerbation rate, week 0-24	Placebo	76	0.63 (NA)							Statistical differences between group baseline characteristics were tested using the F-test, chi-squared test and Fisher's exact test, as appropriate. Rate of clinically significant asthma exacerbations over 24 and 52 weeks were compared between treatment groups using a two-sided test at a=0.05 with a generalized Poisson regression model. The rate ratio (RR) of exacerbations between the treatment groups and 95% confidence interval (CI) were obtained.	
Clinically significant asthma exacerbation rate, week 0-52	Omalizumab	159	0.73 (NA)	0.71	0.59-0.83	<0.001	RR: 0.504	0.350, 0.725	<0.001	Statistical differences between group baseline characteristics were tested using the F-test, chi-squared test and Fisher's exact test, as appropriate. Rate of clinically significant asthma exacerbations over 24 and 52 weeks were compared between treatment groups using a two-sided test at a=0.05 with a generalized Poisson regression model. The rate ratio (RR) of exacerbations between the treatment groups and 95% confidence interval (CI) were obtained.	(16)
	Placebo	76	1.44 (NA)								
% reduction in ICS dose during the steroid-adjustable phase	Omalizumab	159	2.5 (NA)	0.5	NA	NA	NA	NA	NA	The percentage change from baseline in ICS dose was compared using the van Elteren test: a nonparametric test that compares treatments in the presence of blocking (an extension of Wilcoxon's rank-sum test)41; percent change in ICS dose for patients who discontinued before the 28-	(16)
	Placebo	76	2.0 (NA)								

Results of OMALIZUMAB (NCT00079937) for severe allergic asthma											
										week adjustable-steroid phase was imputed as zero.	
Clinically significant asthma exacerbation rate, week 25-52	Omalizumab	159	0.29 (NA)	-0.48	-0.60, -0.36	<0.001 NA	RR: 0.372	0.243, 0.568	<0.001	Statistical differences between group baseline characteristics were tested using the F-test, chi-squared test and Fisher's exact test, as appropriate. Rate of clinically significant asthma exacerbations over 24 and 52 weeks were compared between treatment groups using a two-sided test at a=0.05 with a generalized Poisson regression model. The rate ratio (RR) of exacerbations between the treatment groups and 95% confidence interval (CI) were obtained.	(16)
	Placebo	76	0.77 (NA)								
Rate of clinically significant exacerbations over 52 weeks in patients with baseline percent predicted FEV1 <80%	Omalizumab	61	0.84 (NA)	-0.8	-0.96, -0.64	<0.001	RR: 0.512	0.315, 0.833	0.007	Statistical differences between group baseline characteristics were tested using the F-test, chi-squared test and Fisher's exact test, as appropriate. Rate of clinically significant asthma exacerbations over 24 and 52 weeks were compared between treatment groups using a two-sided test at a=0.05 with a generalized Poisson regression model. The rate ratio (RR) of exacerbations between the treatment groups and 95% confidence interval (CI) were obtained.	(16)
	Placebo	28	1.64 (NA)								
Rate of clinically significant	Omalizumab	54	0.66 (NA)	-0.69	-0.79, -0.59	<0.001	RR: 0.455	0.279, 0.854	0.012	Statistical differences between group baseline characteristics were tested using the F-test, chi-squared test and	
	Placebo	35	1.35 (NA)								

Results of OMALIZUMAB (NCT00079937) for severe allergic asthma										
exacerbations over 52 weeks in patients with baseline percent predicted FEV1 ≥80%									Fisher's exact test, as appropriate. Rate of clinically significant asthma exacerbations over 24 and 52 weeks were compared between treatment groups using a two-sided test at a=0.05 with a generalized Poisson regression model. The rate ratio (RR) of exacerbations between the treatment groups and 95% confidence interval (CI) were obtained.	
AE, n (%)	Omalizumab	166	155 (93.4)	-1.6	-7.72; - 4.47	0.779	0.98	0.92 - 1.05	0.6125	Assessment of safety was based on the frequency of all AEs. Statistical differences between the frequency of AEs reported in the omalizumab and placebo groups were calculated using Fisher's exact test	(25)
	Placebo	80	76 (95.0)								
SAE, n (%)	Omalizumab	166	2 (1.2)	1.20%	-0.45% - 2.86%)	0.1553	2.42	0.12 – 49.77	0.5791	Assessment of safety was based on the frequency of all AEs. Statistical differences between the frequency of AEs reported in the omalizumab and placebo groups were calculated using Fisher's exact test 0.5 added to all cells in 2x2, to calculate relative differences as 0 events occurred in placebo arm.	(16)
	Placebo	80	0 (0)								
Discontinued due to AE, n (%)	Omalizumab	166	6 (3.6)	-6.39	(-13.55; 0.78)	0.0801	0.36	(0.13 - 1.01)	0.0511	Assessment of safety was based on the frequency of all AEs. Statistical differences between the frequency of AEs reported in the omalizumab and placebo	(16)
	Placebo	80	8 (10.0)								

Results of OMALIZUMAB (NCT00079937) for severe allergic asthma	
	groups were calculated using Fisher's exact test

Table 96. Results of Lanier et al., 2009 (NCT00079937) for severe allergic asthma(15)

Results of Omalizumab (NCT00079937) for severe allergic asthma											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Change from BL at week 24 of PAQLQ-IA global score*	Omalizumab	NA	NA	0.04	NA	0.676	NA	NA	NA	*PAQLQ overall score was compared by using an analysis of covariance; missing data were imputed by using the last available assessments.* *The level of statistical significance was adjusted for secondary efficacy endpoints, based on the hierarchical Hochberg multiple testing procedure*	(15)
	Placebo	NA	NA								

Severe eosinophilic asthma

Table 97. Results of Liberty Asthma VOYAGE (NCT02948959) for severe eosinophilic asthma

Results of Liberty Asthma VOYAGE (NCT02948959) for severe eosinophilic asthma											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Annualized rate of severe asthma exacerbations during 52-week treatment period	Dupilumab	212	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	The annualized rate of severe exacerbation events was analyzed using a negative binominal regression model that includes the total number of events observed from randomization up to week 52 or last study contact date (whichever comes earlier) as the response variable, and includes treatment group, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, and number of severe exacerbation events within 1 year prior to the study as covariates, and log-transformed standardized observation duration as an offset variable.	(24)
	Placebo	107	[redacted]								
% experience no exacerbation during 52-week treatment periods, %	Dupilumab	212	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	All severe exacerbation events occurred during the 52-week treatment period are included, regardless of whether the patient is on-treatment or not OR, RR and RD are derived from a logistic regression model with treatment, age, weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, and number of severe exacerbation events within 1 year prior to the study as covariates.	(24)
	Placebo	107	[redacted]								
	Dupilumab	212	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Change from baseline in percentage of predicted FEV1 was analyzed using a	(24)

Results of Liberty Asthma VOYAGE (NCT02948959) for severe eosinophilic asthma														
Change from BL at week 12 of ppFEV1, (±SE)	Placebo	107	[redacted]										mixed-effect model with repeated measures approach, including treatment, baseline weight, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment-by-visit interaction, baseline percentage of predicted FEV1 value, and baseline-by-visit interaction as covariates.	
% patients with >=200mL improvement in FEV1 at week 12 (95% CI)	Dupilumab	212	[redacted]										RR and RD are derived from a logistic regression model with treatment, age, weight group, region, baseline eosinophil level, baseline ICS dose level, and baseline pre-bronchodilator FEV1 as covariates. Patients with missing pre-bronchodilator FEV1 at W12 were considered as no improvement.	(24)
	Placebo	107	[redacted]											
Change from BL in ACQ-7-IA, (±SE)	Dupilumab	212	[redacted]										Derived from MMRM model with change from baseline in ACQ-7-IA up to Week 24 as the response variable, and treatment, age, weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline ACQ-7-IA and baseline-by-visit interaction as covariates.	(24)
	Placebo	107	[redacted]											
Change from BL at week 52 of PAQLQ-IA global score	Dupilumab	212	[redacted]										Derived from MMRM model with change from baseline in PAQLQ(S)-IA global score values up to Week 52 as the response variable, and treatment, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline PAQLQ(S)-IA global score and baseline-by-visit interaction as covariates.	(27)
	Placebo	107	[redacted]											

Results of Liberty Asthma VOYAGE (NCT02948959) for severe eosinophilic asthma											
Change from BL at week 52 of PRQLQ global score (+SE)	Dupilumab	212	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Derived from MMRM model with change from baseline in PAQLQ(S)-IA global score values up to Week 52 as the response variable, and treatment, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline PAQLQ(S)-IA global score and baseline-by-visit interaction as covariates.	(27)
	Placebo	107	[redacted]								
AE, n (%)	Dupilumab	271	225 (83.0)	3.18%	(-4.96% - 11.31%)	NA	1.04	(0.94 - 1.15)	0.4565	The safety variables, including AEs, laboratory parameters, vital signs, ECG, and physical examinations will be summarized using descriptive statistics.	(27)
	Placebo	134	107 (79.9)								
SAE, n (%)	Dupilumab	271	13 (4.8)	0.32%	(-4.01% - 4.65%)	NA	1.07	(0.42 - 2.76)	0.8950		(27)
	Placebo	134	6 (4.5)								
AEs leading to discontinuation, n (%)	Dupilumab	271	5 (1.8)	0.35%	(-2.25% - 2.96%)	NA	1.24	(0.24 - 6.29)	0.8103		(27)
	Placebo	134	2 (1.5)								

Table 98. Results of MEPOLIZUMAB (NCT02377427) for severe eosinophilic asthma

Results of MEPOLIZUMAB (NCT02377427) for severe eosinophilic asthma											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		

Results of MEPOLIZUMAB (NCT02377427) for severe eosinophilic asthma											
$AUC_{(0\text{-}inf)}$ (µg · day/mL)	Mepolizumab 40mg	26	454.4 (422.1, 486.7)	NA	NA	NA	NA	NA	NA	*Mepolizumab plasma PK concentrations were analyzed by nonlinear mixed-effect modeling methods (SAS Institute Inc, Cary, NC). A two-compartment model with first-order absorption and elimination was used with PK distribution parameters and bioavailability fixed to previously estimated adult values. Bodyweight was incorporated into the model using physiological allometry with allometric exponents for clearance and volumes estimated. Final model appropriateness was assessed using goodness of fit plots, simulations, and statistical test*	(18)
	Mepolizumab 100mg	10	675.2 (602.2, 748.2)								
	Mepolizumab 40/100mg	NA	NA								
C_{max} (µg/mL)	Mepolizumab 40mg	26	10.2 (9.5, 10.9)	NA	NA	NA	NA	NA	NA	*Mepolizumab plasma PK concentrations were analyzed by nonlinear mixed-effect modeling methods (SAS Institute Inc, Cary, NC). A two-compartment model with first-order absorption and elimination was used with PK distribution parameters and bioavailability fixed to previously estimated adult values. Bodyweight was incorporated into the model using physiological allometry with allometric exponents for clearance and volumes estimated. Final model appropriateness was assessed using goodness of fit plots, simulations, and statistical test*	(18)
	Mepolizumab 100mg	10	16.3 (15.0, 17.6)								
	Mepolizumab 40/100mg	NA	NA								
$C_{max\ SS}$ (µg/mL)	Mepolizumab 40mg	26	17.8 (15.3, 20.2)	NA	NA	NA	NA	NA	NA	*Mepolizumab plasma PK concentrations were analyzed by nonlinear mixed-effect modeling methods (SAS Institute Inc, Cary, NC). A two-compartment model with first-order absorption and elimination was used with PK distribution parameters and bioavailability fixed to previously estimated adult values. Bodyweight was incorporated into the model using physiological allometry with allometric exponents for clearance and volumes estimated. Final model appropriateness was*	(18)
	Mepolizumab 100mg	10	28.5 (25.0, 31.9)								
	Mepolizumab 40/100mg	NA	NA								

Results of MEPOLIZUMAB (NCT02377427) for severe eosinophilic asthma											
										assessed using goodness of fit plots, simulations, and statistical test	
CL/F (L/day)	Mepolizumab 40mg	26	0.09 (0.08, 0.09)	NA	NA	NA	NA	NA	NA	*Mepolizumab plasma PK concentrations were analyzed by nonlinear mixed-effect modeling methods (SAS Institute Inc, Cary, NC). A two-compartment model with first-order absorption and elimination was used with PK distribution parameters and bioavailability fixed to previously estimated adult values. Bodyweight was incorporated into the model using physiological allometry with allometric exponents for clearance and volumes estimated. Final model appropriateness was assessed using goodness of fit plots, simulations, and statistical test*	(18)
	Mepolizumab 100mg	10	0.15 (0.13, 0.16)								
	Mepolizumab 40/100mg	NA	NA								
C_{av} *(µg/mL)*	Mepolizumab 40mg	26	16.2 (15.1, 17.4)	NA	NA	NA	NA	NA	NA	*Mepolizumab plasma PK concentrations were analyzed by nonlinear mixed-effect modeling methods (SAS Institute Inc, Cary, NC). A two-compartment model with first-order absorption and elimination was used with PK distribution parameters and bioavailability fixed to previously estimated adult values. Bodyweight was incorporated into the model using physiological allometry with allometric exponents for clearance and volumes estimated. Final model appropriateness was assessed using goodness of fit plots, simulations, and statistical test*	(18)
	Mepolizumab 100mg	10	24.1 (21.5, 26.7)								
	Mepolizumab 40/100mg	NA	NA								
$t_{½}$ *(days)*	Mepolizumab 40mg	26	23.6 (21.9, 25.3)	NA	NA	NA	NA	NA	NA	*Mepolizumab plasma PK concentrations were analyzed by nonlinear mixed-effect modeling methods (SAS Institute Inc, Cary, NC). A two-compartment model with first-order absorption and elimination was used with PK distribution parameters and bioavailability fixed to previously estimated adult values. Bodyweight was incorporated into the model using physiological allometry with allometric exponents for clearance and volumes*	(26)
	Mepolizumab 100mg	10	21.8 (19.6, 24.1)								
	Mepolizumab 40/100mg	NA	NA								

Results of MEPOLIZUMAB (NCT02377427) for severe eosinophilic asthma											
										estimated. Final model appropriateness was assessed using goodness of fit plots, simulations, and statistical test	
Blood eosinophil count, cells/µL, week 12/ % reduction from BL at week 12	Mepolizumab 40mg	26	42 (26, 67)/ 88.5%	NA	NA	NA	NA	NA	NA	*The ratio of blood eosinophil count at week 12 to baseline was summarized descriptively, and the ratio at each visit to baseline presented graphically. Bodyweight-adjusted apparent clearance point estimates with 90% CIs in children 6 to 11 years were presented alongside the historical estimated adult value of 0.29 L/day (unpublished data) with a proposed 80% to 125% interval around this estimate of 0.23 to 0.36 L/day*	(26)
	Mepolizumab 100mg	10	55 (31, 97)/ 83.4%								
	Mepolizumab 40/100mg	NA	NA								
ACQ-7	Mepolizumab 40mg	26	-0.55 (-1.01, -0.09)[a] -0.65 (-1.15, -1.16)[b] -0.41 (-0.91, 0.08)[c] 11/23 (48%)[d]	NA	NA	NA	NA	NA	NA	*For blood eosinophil counts and asthma control questionnaire scores, baseline was defined as the value recorded before the first mepolizumab treatment in part A (overall study week 0). All statistical analyses were performed with SAS software (version 9.4; SAS Institute, Cary, NC)*	(26)
	Mepolizumab 100mg	10	-0.47 (-1.16, 0.21)[a] -0.30(-1.19, 0.59)[b] 0.08 (-0.88, 1.04)[c]								

Results of MEPOLIZUMAB (NCT02377427) for severe eosinophilic asthma											
			5/10 (50%)[d]								
	Mepolizumab 40/100mg	NA	NA								
C-ACT	Mepolizumab 40mg	26	1.8 (0.2, 3.5)[a] 3.0 (0.7, 5.4)[b] 2.1 (0.2, 4.1)[c]	NA	NA	NA	NA	NA	NA	*For blood eosinophil counts and asthma control questionnaire scores, baseline was defined as the value recorded before the first mepolizumab treatment in part A (overall study week 0). All statistical analyses were performed with SAS software (version 9.4; SAS Institute, Cary, NC)*	(26)
	Mepolizumab 100mg	10	2.4 (-0.9, 5.7)[a] 1.5 (-1.6, 4.6)[b] -0.3 (-4.0, 3.4)[c]								
	Mepolizumab 40/100mg	NA	NA								
Prebronchodilator FEV_1 (mL)	Mepolizumab 40mg	26	93 (-19, 206)[a] 90 (-17, 198)[b] 72 (-37, 181)[c]	NA	NA	NA	NA	NA	NA	*NA*	(26)
	Mepolizumab 100mg	10	55 (-52, 162)[a] -63 (-314, 188)[b] 2 (-175, 179)[c]								
	Mepolizumab 40/100mg	NA	NA								
Patients with on-	Mepolizumab 40mg	26	8 (31)[e] 6 (23)[f]	NA	NA	NA	NA	NA	NA	*NA*	(26)

Results of MEPOLIZUMAB (NCT02377427) for severe eosinophilic asthma											
treatment exacerbations (week 0-12), n (%)			2 (8)[g]								
	Mepolizumab 100mg	10	2 (20)[e] 1 (10)[f] 1 (10)[g]								
	Mepolizumab 40/100mg	NA	NA								
Serum total IL-5 levels, ng/L	Mepolizumab 40mg	26	137.1 (NA)	NA	NA	NA	NA	NA	NA	*NA*	(26)
	Mepolizumab 100mg	10	96.4 (NA)								
	Mepolizumab 40/100mg	NA	NA								
AE, n(%)	Mepolizumab 40mg	16	15 (94)	NA	NA	NA	NA	NA	NA	*All statistical analyses were performed by using the safety population (all children who received ≥1 dose of mepolizumab within part B). Endpoints were summarized by using appropriate descriptive statistics (mean/geometric mean, median, SD, and range). AEs were summarized by using the Medical Dictionary for Regulatory Activities Primary System Organ Class and Preferred Terms. Annualized exacerbation rates were determined by using a negative binomial generalized linear model with logarithm of time as an offset variable, from which estimated rates per year and 95% CIs were calculated.*	(51)
	Mepolizumab 100mg	10	8 (80)								
	Mepolizumab 40/100mg	4	4 (100)								
Treatment-	Mepolizumab 40mg	16	4 (25)	NA	NA	NA	NA	NA	NA	*All statistical analyses were performed by using the safety population (all children who received ≥1 dose of mepolizumab*	(51)

Results of MEPOLIZUMAB (NCT02377427) for severe eosinophilic asthma											
related on-treatment AEs	Mepolizumab 100mg	10	3 (3)							*within part B). Endpoints were summarized by using appropriate descriptive statistics (mean/geometric mean, median, SD, and range). AEs were summarized by using the Medical Dictionary for Regulatory Activities Primary System Organ Class and Preferred Terms. Annualized exacerbation rates were determined by using a negative binomial generalized linear model with logarithm of time as an offset variable, from which estimated rates per year and 95% CIs were calculated.*	
	Mepolizumab 40/100mg	4	1 (25)								
AE leading to discontinuation of treatment	Mepolizumab 40mg	16	0	NA	NA	NA	NA	NA	NA	*All statistical analyses were performed by using the safety population (all children who received ≥1 dose of mepolizumab within part B). Endpoints were summarized by using appropriate descriptive statistics (mean/geometric mean, median, SD, and range). AEs were summarized by using the Medical Dictionary for Regulatory Activities Primary System Organ Class and Preferred Terms. Annualized exacerbation rates were determined by using a negative binomial generalized linear model with logarithm of time as an offset variable, from which estimated rates per year and 95% CIs were calculated.*	(51)
	Mepolizumab 100mg	10	0								
	Mepolizumab 40/100mg	4	0								
SAE, n (%)	Mepolizumab 40mg	16	5 (31)	NA	NA	NA	NA	NA	NA	*All statistical analyses were performed by using the safety population (all children who received ≥1 dose of mepolizumab within part B). Endpoints were summarized by using appropriate descriptive statistics (mean/geometric mean, median, SD, and range). AEs were summarized by using the Medical Dictionary for Regulatory Activities Primary System Organ Class and Preferred Terms. Annualized exacerbation rates were determined by using a negative binomial generalized linear model with logarithm of time as an offset*	(51)
	Mepolizumab 100mg	10	3 (30)								
	Mepolizumab 40/100mg	4	1 (25)								

Results of MEPOLIZUMAB (NCT02377427) for severe eosinophilic asthma											
										variable, from which estimated rates per year and 95% CIs were calculated.	
Blood eosinophil count, cells/µL, geometric mean (SD log), week 52	Mepolizumab 40mg	16	48 (0.858)	NA	NA	NA	NA	NA	NA	*For blood eosinophil counts, the ratio to baseline was summarized by visit; if a result of zero was recorded, a small value (half the minimum nonzero result) was imputed before log-transformation. For blood eosinophil counts and asthma control questionnaire scores, baseline was defined as the value recorded before the first mepolizumab treatment in part A (overall study week 0). All statistical analyses were performed with SAS software (version 9.4; SAS Institute, Cary, NC)*	(51)
	Mepolizumab 100mg	10	44 (1.022)								
	Mepolizumab 40/100mg	4	47 (0.841)								

[a] Change from BL at week 4, [b] Change from BL at week 8, [c] Change from BL at week 12, [d] ≥0.5 point reduction from BL, n/N (%), [e] Any on treatment exacerbation, [f] 1 exacerbation, [g] 2 exacerbations

Severe asthma with elevated FeNO

Table 99. Results of Liberty Asthma VOYAGE (NCT02948959) for severe asthma with elevated FeNO

Results of Liberty Asthma VOYAGE (NCT02948959) for severe asthma with elevated FeNO											
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Annualized rate of severe asthma exacerbations	Dupilumab	254	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	The annualized rate of severe exacerbation events was analyzed using a negative binominal regression model that includes the total number of events observed from randomization up to week 52 or last study contact date (whichever comes earlier) as the response variable, and includes treatment group, age, baseline weight group, region, baseline eosinophil level, baseline	(24)
	Placebo	130	[redacted]								

Results of Liberty Asthma VOYAGE (NCT02948959) for severe asthma with elevated FeNO														
during 52-week treatment period													FeNO level, baseline ICS dose level, and number of severe exacerbation events within 1 year prior to the study as covariates, and log-transformed standardized observation duration as an offset variable.	
% experience no exacerbation during 52-week treatment periods, %	Dupilumab	254	[redacted]										The change from baseline for continuous endpoints was analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model included change from baseline as response variables, and for treatment, age, weight (≤30kg, >30kg), region, baseline eosinophil level (<150 cells/µL, 50 – 299 cells/µL, and ≥300 cells/µL), ICS (medium/high) strata, visit, treatment-by-visit interaction, baseline value, and baseline-by-visit interaction as covariates. Sex, height, and ethnicity was also included as covariates in the models for spirometry parameters. An unstructured correlation matrix was used to model the within-patient errors. Parameters was estimated using restricted maximum likelihood method using the Newton-Raphson algorithm. Statistical inferences on treatment comparisons for the change in percentage from baseline at Weeks 12 was derived from the mixed-effect model with Kenward and Roger degree of freedom a justment approach.	(24)
	Placebo	130	[redacted]											
Change from BL at week 12 of ppFEV1, (±SE)	Dupilumab	254	[redacted]										Change from baseline in percentage of predicted FEV1 was analyzed using a mixed-effect model with repeated measures approach, including treatment, baseline weight, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment-by-visit interaction, baseline percentage of predicted FEV1 value, and baseline-by-visit interaction as covariates.	(24)
	Placebo	130	[redacted]											

Results of Liberty Asthma VOYAGE (NCT02948959) for severe asthma with elevated FeNO												
% patients with >=200mL improvement in FEV1 at week 12 (95% CI)	Dupilumab	254	[redacted]								RR and RD are derived from a logistic regression model with treatment, age, weight group, region, baseline eosinophil level, baseline ICS dose level, and baseline pre-bronchodilator FEV1 as covariates. Patients with missing pre-bronchodilator FEV1 at W12 were considered as no improvement.	(24)
	Placebo	130	[redacted]									
Change from BL in ACQ-7-IA, (±SE)	Dupilumab	254	[redacted]								Derived from MMRM model with change from baseline in ACQ-7-IA up to Week 24 as the response variable, and treatment, age, weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline ACQ-7-IA and baseline-by-visit interaction as covariates.	(24)
	Placebo	130	[redacted]									
Change from BL at week 52 of PAQLQ-IA global score	Dupilumab	254	[redacted]								Derived from MMRM model with change from baseline in PAQLQ(S)-IA global score values up to Week 52 as the response variable, and treatment, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline PAQLQ(S)-IA global score and baseline-by-visit interaction as covariates.	(27)
	Placebo	130	[redacted]									
Change from BL at week 52 of PRQLQ	Dupilumab	254	[redacted]								Derived from MMRM model with change from baseline in PAQLQ(S)-IA global score values up to Week 52 as the response variable, and treatment, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction,	(27)
	Placebo	130	[redacted]									

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Results of Liberty Asthma VOYAGE (NCT02948959) for severe asthma with elevated FeNO											
global score (+SE)										baseline PAQLQ(S)-IA global score and baseline-by-visit interaction as covariates.	
AE, n (%)	Dupilumab	271	225 (83.0)	3.18%	(-4.96% - 11.31%)	NA	1.04	(0.94 - 1.15)	0.4565	The safety variables, including AEs, laboratory parameters, vital signs, ECG, and physical examinations will be summarized using descriptive statistics.	(27)
	Placebo	134	107 (79.9)								
SAE, n (%)	Dupilumab	271	13 (4.8)	0.32%	(-4.01% - 4.65%)	NA	1.07	(0.42 - 2.76)	0.8950		(27)
	Placebo	134	6 (4.5)								
AEs leading to discontinuation, n (%)	Dupilumab	271	5 (1.8)	0.35%	(-2.25% - 2.96%)	NA	1.24	(0.24 - 6.29)	0.8103		(27)
	Placebo	134	2 (1.5)								

Non-allergic asthma with high EOS or high FeNO

Table 100 Non-allergic asthma with high EOS or high FeNO

Results of Liberty Asthma VOYAGE (NCT02948959) for non-allergic asthma with high EOS or high FeNO											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Annualized rate of	Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	All severe exacerbation events occurred during the 52-week treatment period are	(24)

Results of Liberty Asthma VOYAGE (NCT02948959) for non-allergic asthma with high EOS or high FeNO

severe asthma exacerbations during 52-week treatment period	Placebo	[redacted]	[redacted]							included, regardless of whether the patient is on-treatment or not The total number of events that occurred during the 52-week treatment period divided by the total number of patient-years followed in the 52-week treatment period. Derived using negative binomial model with the total number of events onset from randomization up to Week 52 visit or last contact date (whichever comes earlier) as the response variable, with the treatment group, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study as covariates, and log-transformed standardized observation duration as an offset variable.	
% experience no exacerbation during 52-week treatment periods, %	Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	All severe exacerbation events occurred during the 52-week treatment period are included, regardless of whether the patient is on-treatment or not OR, RR and RD are derived from a logistic regression model with treatment, age, weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, and number of severe exacerbation events within 1 year prior to the study as covariates	(24)
	Placebo	[redacted]	[redacted]								
Change from BL at week 12 of ppFEV1, (±SE)	Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Derived from MMRM model with change from baseline in Pre-bronchodilator % predicted FEV1 values up to Week 12 as the response variable, and treatment, baseline weight group, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline Pre-bronchodilator % predicted FEV1 value	(24)
	Placebo	[redacted]	[redacted]								

Results of Liberty Asthma VOYAGE (NCT02948959) for non-allergic asthma with high EOS or high FeNO											
										and baseline-by-visit interaction as co-variates	
% patients with >=200mL improve-ment in FEV1 at week 12 (95% CI)	Dupilumab	[redacted]								RR and RD are derived from a logistic re-gression model with treatment, age, weight group, region, baseline eosinophil level, baseline ICS dose level, and base-line pre-bronchodilator FEV1 as covari-ates. Patients with missing pre-bronchodilator FEV1 at W12 were considered as no im-provement.	(24)
	Placebo	[redacted]									
Change from BL in ACQ-7-IA, (±SE)	Dupilumab	[redacted]								Derived from MMRM model with change from baseline in ACQ-7-IA up to Week 24 as the response variable, and treatment, age, weight group, region, baseline eosin-ophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit in-teraction, baseline ACQ-7-IA and base-line-by-visit interaction as covariates.	(24)
	Placebo	[redacted]									
Change from BL at week 52 of PAQLQ-IA global score	Dupilumab	[redacted]								Derived from MMRM model with change from baseline in PAQLQ(S)-IA global score values up to Week 52 as the response vari-able, and treatment, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline PAQLQ(S)-IA global score and baseline-by-visit interaction as covariates.	(27)
	Placebo	[redacted]									
Change from BL at week 52 of PRQLQ	Dupilumab	[redacted]								Derived from MMRM model with change from baseline in PAQLQ(S)-IA global score values up to Week 52 as the response vari-able, and treatment, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction,	(27)
	Placebo	[redacted]									

Results of Liberty Asthma VOYAGE (NCT02948959) for non-allergic asthma with high EOS or high FeNO											
global score (+SE)										baseline PAQLQ(S)-IA global score and baseline-by-visit interaction as covariates.	
AE, n (%)	Dupilumab	271	225 (83.0)	3.18%	(-4.96% - 11.31%)	NA	1.04	(0.94 - 1.15)	0.4565	The safety variables, including AEs, laboratory parameters, vital signs, ECG, and physical examinations will be summarized using descriptive statistics.	(27)
	Placebo	134	107 (79.9)								
SAE, n (%)	Dupilumab	271	13 (4.8)	0.32%	(-4.01% - 4.65%)	NA	1.07	(0.42 - 2.76)	0.8950		(27)
	Placebo	134	6 (4.5)								
AEs leading to discontinuation, n (%)	Dupilumab	271	5 (1.8)	0.35%	(-2.25% - 2.96%)	NA	1.24	(0.24 - 6.29)	0.8103		(27)
	Placebo	134	2 (1.5)								

Appendix E Safety data for intervention and comparator(s)

See section 0 for all safety data for intervention and comparators.

Additional table regarding treatment emergent adverse events leading to permanent treatment discontinuation:

Table 101. [redacted]

[redacted]

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Appendix F Comparative analysis of efficacy and safety

Ultimately, a total of three trials were assessed for patient characteristics one evaluating treatment with dupilumab [VOYAGE; NCT02948959], and two other consisting of omalizumab trials [IA05: NCT00079937 and ICATA: NCT00377572]) were assessed for patient characteristics wherein major differences were observed with regards to key characteristics, including the presence of allergic phenotype via a positive skin prick test or a positive in vitro response to ≥1 perennial allergen in the omalizumab trials, and differences in baseline EOS, ppFEV1, and prior exacerbations and lack of reporting was observed for ICATA (Table 102). These differences were believed to be a potential source of bias to the ITC; hence the main analyses were presented narratively.

In order to account for any potential bias that differences in patient characteristics may cause, a subgroup of patients from VOYAGE was derived via post hoc analyses. The 'omalizumab-eligible' subgroup attempted to better align patients from VOYAGE with those in the IA05 trial, based on an allergic phenotype and corresponding to the inclusion criteria of IA05, which was defined by:

- Baseline weight between 20-150 kg and serum IgE level of 30 to 1300 IU/mL and weight-IgE values combinations based on omalizumab dosing table
- At least 1 positive perennial allergen-specific IgE (concentration >=0.35 IU/mL) among the following allergens: Alternaria tenuis/alternata; Cladosporium herbarum/hormodendrum; Aspergillus Fumigatus; Cat Dander; D. Farinae; D. Pteronyssinus; Dog Dander; German Cockroach

It should be noted that the allergic phenotype in IA05 was based on skin prick test or a positive in vitro response to ≥1 perennial allergen. These tests were not performed as part of the VOYAGE trial, and therefore the presence of 1 positive perennial allergen-specific IgE was used as a proxy for the allergic phenotype in IA05.

In attempt to account for differences in the definition of severe exacerbations that may lead to bias, a similar approach was used, wherein post hoc analyses of VOYAGE were carried out. The modified definition from VOYAGE (deterioration of asthma) was validated by clinical experts as being more comparable to primary exacerbation outcome in IA05 defined as "clinically significant asthma exacerbations." The caveat was that VOYAGE did not allow for doubling of ICS, as permitted in IA05. The outcome definitions, observed placebo rates, and annualized RRs are presented in presented in Table 103.

In summary, two studies (VOYAGE and IA05) were deemed appropriate for the exploratory ITCs, and the inclusion of one additional study (ICATA) was explored for severe exacerbations, which was the only commonly reported outcome from this trial for patients age 6-11 years. The network of connected trials suitable for ITC is displayed in Figure 20. Analyses of severe exacerbations excluding the ICATA3 trial were performed given the limited reporting of baseline characteristics and differences in the study design and population in ICATA.

Table 102 Patient Characteristics of Trials and Subgroups included in the ITCs

Trial Name	Treatment Arm	N	Age, [Range] Mean (SD)	Age, Mean (SD), Range	Male, %	White, %	Baseline EOS (Cells/uL), Mean (SD)	Baseline FeNO, Mean (SD)	Exacerbations in Previous Year, Mean (SD)	Baseline IgE, Mean (SD)	$ppFEV_1$, Mean (SD)
VOYAGE ITT[1]	Dupilumab 100-200 mg Q2W										
	Placebo										
VOYAGE Omalizumab-eligible	Dupilumab 100-200 mg Q2W										
	Placebo										
IA05[210] ITT	Omalizumab 75-375mg Q1M/Q2M										
	Placebo										

Abbreviations: EOS = eosinophil; FeNO = fractional exhaled nitric oxide; IgE = immunoglobulin E; ppFEV1 = percent predicted forced expiratory volume in one second; Q1M = once a month; Q2M = twice a month; Q2W = every two weeks; SD = standard deviation

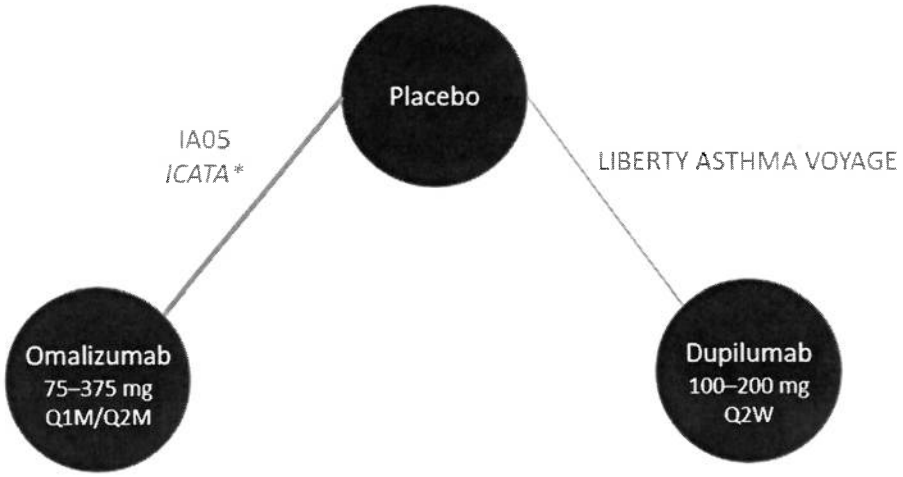
Table 103. Severe Exacerbation Outcomes

Trial	Outcome	Outcome Definition	Timepoint (Weeks)	Annualized Rate in Placebo Arm	Annualized Rate Ratio (95% CI)
VOYAGE[1] **ITT**	Severe exacerbations	Deterioration of asthma requiring any of the following: • Systemic corticosteroids for ≥3 days • Hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids	52	[redacted]	[redacted]
VOYAGE Omalizumab-eligible[1]	Severe exacerbations	Deterioration of asthma requiring any of the following: • Systemic corticosteroids for ≥3 days • Hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids	52	[redacted]	[redacted]
VOYAGE[1] **ITT**	Deterioration of asthma	Deterioration of asthma resulting in any of the following: • Systemic corticosteroids for ≥3 days • Increased ICS dose ≥4 times that at Visit 2	52	[redacted]	[redacted]
VOYAGE Omalizumab-eligible[1]	Deterioration of asthma	Deterioration of asthma resulting in any of the following: • Systemic corticosteroids for ≥3 days • Increased ICS dose ≥4 times that at Visit 2	52	[redacted]	[redacted]
IA05 [2 51]	Severe exacerbations	Worsening of asthma symptoms requiring any of the following: • Systemic corticosteroids for ≥3 days • Doubling of baseline ICS dose	24 52†	1.40 1.36	0.69 (0.53, 0.90) 0.57 (0.45, 0.72)†

† Data not included in ITC given that the study design included an ICS dose reduction phase after 24-weeks.

Abbreviations: BDP = beclomethasone dipropionate; CI = confidence interval; ICS = inhaled corticosteroid; NA = not applicable

Figure 20 Network Diagram



*Data from the ICATA trial will be included in a set of analyses for severe exacerbations only
Abbreviations: Q1M = once a month; Q2M = twice a month; Q2W = every two weeks

Exploratory Bucher ITCs based on the ITT (as randomized, all patients) and omalizumab-eligible populations from VOYAGE and IA05 were performed for the following outcomes of interest:

- Severe exacerbations (annualized rates)
- Deterioration of asthma from VOYAGE (post hoc analysis) vs. severe exacerbations from IA05 (annualized rates)
- Morning asthma symptom score at 24 weeks
- Change in PAQLQ(S)-IA at 24 weeks
- Discontinuations due to AEs at 52 weeks

The following section presents the key findings of the exploratory ITCs comparing dupilumab (100–200 mg Q2W) in the VOYAGE trial to omalizumab (75–375 mg Q1M or Q2M) in the IA05 trial. Results for dupilumab versus omalizumab are presented in Table 104. Note that given the differences observed across the included studies with regards to patient characteristics and definitions of severe exacerbations, findings of these analyses should be interpreted with caution.

12.4.1 ITT Population

The exploratory ITC results for the ITT population suggest that dupilumab has a numerical advantage over omalizumab in improving annualized rates of severe exacerbations (RR [95% CI]: 0.66 [0.42, 1.06]) and deterioration of asthma (RR [95% CI]: 0.66 [0.42, 1.03]) (Table 104). However, comparable effects on change from baseline in morning asthma score, rescue medication use (puffs per day), and PAQLQ(S)-IA were seen for both treatment groups at Week 24 (Table 104). The rates of discontinuations due to AEs were also similar for dupilumab and omalizumab following 52 weeks of treatment (Table 104).

For the sensitivity analyses of severe exacerbations (unadjusted, un-annualized) for the ITT population, dupilumab had a numerical advantage over omalizumab in improving severe exacerbations (RR [95% CI]: 0.67 [0.44, 1.04]). These results were based on the RE model, although no statistical heterogeneity was identified (i.e., the estimate of between-study variance was 0, I2 = 0%), hence the pooled estimate from the random-effect model was identical to the one from obtained from the fixed-effect analysis.

12.4.2 Omalizumab-eligible Population

The ITC results based on the omalizumab-eligible population were similar to the results based on the ITT population across all analyzed outcomes. The results suggest that dupilumab provides a numerical advantage over omalizumab in

improving annualized rates of severe exacerbations (RR [95% CI]: 0.60 [0.32, 1.13]) and deterioration of asthma (RR [95% CI]: 0.63 [0.34, 1.16]) (Table 104). No differences in change from baseline in morning asthma score, rescue medication use (puffs per day), and PAQLQ(S)-IA were seen for both treatment groups at Week 24 (Table 104). The rates of discontinuations due to AEs were also similar for dupilumab and omalizumab following 52 weeks of treatment for the omalizumab-eligible populations (Table 104).

Table 104 Bucher ITC Estimates and 95% Confidence Intervals for Dupilumab vs Omalizumab in Pediatric Patients (age 6 to <12 years) with Uncontrolled Moderate-to-Severe Asthma

Outcome	Included trials	ITT	Omalizumab-eligible
Severe Exacerbations (Annualized Rate Ratio)	VOYAGE, IA05		
	VOYAGE IA05, ICATA		
Asthma Deterioration (Annualized Rate Ratio)	VOYAGE, IA05		
Morning Asthma Symptom Score* (Mean Difference in CFB at 24-weeks)	VOYAGE, IA05		
Rescue Medication Puffs Per Day (Mean Difference in CFB at 24-weeks)	VOYAGE, IA05		
PAQLQ(S)-IA (Mean Difference in CFB at 24-weeks)	VOYAGE, IA05		
Discontinuations Due to AEs (OR End of Study)	VOYAGE, IA05		

Abbreviations: CFB = change from baseline; AEs = adverse events; PAQLQ(S)-IA = Pediatric Asthma Quality of Life Questionnaire with Standardized Activities–Interviewer Administered; OR = odds ratio

*Defined based on the outcome definition in VOYAGE, which evaluated participant's overall asthma symptoms experienced during the previous night.

Legend: Numerically favorable (p-value >0.05 and ≤ 0.15) Numerically comparable (p>0.15)

Appendix G – Extrapolation

N/A, no extrapolations.

Appendix H – Literature search for HRQoL data

N/A, no literature search for HRQoL data

Appendix I Mapping of HRQoL data

Utility Analysis

Utility data were collected at baseline, week 24 and week 52 in the VOYAGE trial. EQ-5D-Y score were collected for all patients, however as the instrument is only applicable to children above 8 years old two analyses will be performed:

- Including all patients in the ITT population
- Including only patients 8 years of age or older

This duplicated analysis will be only conducted for the overall trial population in the first instance. Should the utility estimates prove to be similar in the two analyses, further utility analyses for subgroups of patients from VOYAGE will only be conducted on patients of all ages (i.e., NOT restricted to patients 8 years or older). For subgroups that eventually become part of submissions to regulatory authorities, the duplicated analysis may be conducted in order to support the assumption made in the model and to provide as part of the evidence package.

Utility analyses will be performed using on-treatment records, both for the dupilumab and placebo populations.

Analyses of the EQ-5D-Y UK-weighted utility using the UK EQ-5D-3L value set and utility index as a function of treatment, control, and severe or moderate exacerbation and response will be conducted to derive utility values for the health states to be used in the four- and five-sub-state economic model.

Analyses specific to the Danish market will be conducted following the feedback from Danish authorities. Given the concerns regarding the derivation of EQ-5D-5L data from the EQ-5D-Y, Evidera recommended consulting the DMC regarding the acceptability of using the EQ-5D-3L for children and therefore of deviating from the DMC general guidance which favours the EQ-5D-5L. The EQ-5D-Y data from VOYAGE should then be analysed again, using the Danish value set for the EQ-5D-3L, for the purpose of the Danish submission.

Briefly, there is currently no endorsed value set of the EQ-5D-Y to support its use in economic evaluations and the EuroQol group advised against the use of the EQ-5D-3L value sets as a proxy value set for the EQ-5D-Y. In absence of a better option to derive EQ-5D-Y scores in children, the EQ-5D-3L value sets (with Danish tariffs) were used in the base case.

Appendix J Probabilistic sensitivity analyses

	Expected value	Standard error/N*	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)
Proportion of females at model start for Child cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age at model start (in years) for Child cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight (in kg) for Child cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IgE level (in IU/mL) for Child cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with weight <30 kg for Child cohort - 0-1 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with weight <30 kg for Child cohort - 2-3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with weight <30 kg for Child cohort - 4-5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with weight <30 kg for Child cohort - 6-7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with weight <30 kg for Child cohort - 8-9 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with weight <30 kg for Child cohort - 10-11 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with weight <30 kg for Child cohort - 12-13 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with weight <30 kg for Child cohort - 14-15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with weight <30 kg for Child cohort - 16-17 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with weight <30 kg for Child cohort - 18-19 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with weight <30 kg for Child cohort - 20-100 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients using Medium-dose ICS in Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients using High-dose ICS in Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients using Medium-dose ICS/LABA (combination inhaler) in Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients using High-dose ICS/LABA (combination inhaler) in Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients using LABA in Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Proportion of patients using LTRA in Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients using LAMA in Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients using Theophylline in Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients using SABA in Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of responders in Child cohort - Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of responders in Child cohort - Omalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of responders in Child cohort - Mepolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation rate per person-year for Child cohort: while using data from trials conducted in children - Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation rate per person-year for Child cohort: while using data from trials conducted in children - Omalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation rate per person-year for Child cohort: while using data from trials conducted in children - Mepolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation rate per person-year for Child cohort: while using data from trials conducted in adults/adolescents - Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation rate per person-year for Child cohort: while using data from trials conducted in adults/adolescents - Omalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation rate per person-year for Child cohort: while using data from trials conducted in adults/adolescents - Mepolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Background therapy alone - Controlled to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Background therapy alone - Uncontrolled to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Background therapy alone - Moderate Exacerbation to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Background therapy alone - Severe Exacerbation to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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TP for Child cohort: while using data from trials conducted in children - Period 1 - Background therapy alone - Controlled to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Background therapy alone - Uncontrolled to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Background therapy alone - Moderate Exacerbation to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Background therapy alone - Severe Exacerbation to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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TP for Child cohort: while using data from trials conducted in children - Period 1 - Background therapy alone - Severe Exacerbation to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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TP for Child cohort: while using data from trials conducted in children - Period 3 - Background therapy alone - Controlled to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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TP for Child cohort: while using data from trials conducted in children - Period 1 - Dupilumab + background therapy - All patients - Controlled to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Dupilumab + background therapy - All patients - Uncontrolled to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Dupilumab + background therapy - All patients - Moderate Exacerbation to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Dupilumab + background therapy - All patients - Severe Exacerbation to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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TP for Child cohort: while using data from trials conducted in children - Period 1 - Dupilumab + background therapy - All patients - Uncontrolled to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Dupilumab + background therapy - All patients - Moderate Exacerbation to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Dupilumab + background therapy - All patients - Severe Exacerbation to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Dupilumab + background therapy - All patients - Controlled to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Dupilumab + background therapy - All patients - Uncontrolled to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Dupilumab + background therapy - All patients - Moderate Exacerbation to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Dupilumab + background therapy - All patients - Severe Exacerbation to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Dupilumab + background therapy - All patients - Controlled to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Dupilumab + background therapy - All patients - Uncontrolled to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Dupilumab + background therapy - All patients - Moderate Exacerbation to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 1 - Dupilumab + background therapy - All patients - Severe Exacerbation to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - All patients - Controlled to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - All patients - Uncontrolled to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - All patients - Moderate Exacerbation to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - All patients - Severe Exacerbation to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - All patients - Controlled to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - All patients - Uncontrolled to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - All patients - Moderate Exacerbation to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - All patients - Severe Exacerbation to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - All patients - Controlled to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - All patients - Uncontrolled to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - All patients - Moderate Exacerbation to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - All patients - Severe Exacerbation to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - All patients - Controlled to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - All patients - Uncontrolled to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - All patients - Moderate Exacerbation to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - All patients - Severe Exacerbation to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - All patients - Controlled to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - All patients - Uncontrolled to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - All patients - Moderate Exacerbation to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - All patients - Severe Exacerbation to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - All patients - Controlled to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - All patients - Uncontrolled to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - All patients - Moderate Exacerbation to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - All patients - Severe Exacerbation to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - All patients - Controlled to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - All patients - Uncontrolled to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - All patients - Moderate Exacerbation to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - All patients - Severe Exacerbation to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - All patients - Controlled to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - All patients - Uncontrolled to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - All patients - Moderate Exacerbation to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - All patients - Severe Exacerbation to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Controlled to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Uncontrolled to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Moderate Exacerbation to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Severe Exacerbation to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Controlled to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Uncontrolled to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Moderate Exacerbation to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Severe Exacerbation to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Controlled to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Uncontrolled to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Moderate Exacerbation to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Severe Exacerbation to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Controlled to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Uncontrolled to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Moderate Exacerbation to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 2 - Dupilumab + background therapy - Responders only - Severe Exacerbation to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Controlled to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Uncontrolled to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Moderate Exacerbation to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Severe Exacerbation to Controlled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Controlled to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Uncontrolled to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Moderate Exacerbation to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Severe Exacerbation to Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Controlled to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Uncontrolled to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Moderate Exacerbation to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Severe Exacerbation to Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Controlled to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Uncontrolled to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Moderate Exacerbation to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TP for Child cohort: while using data from trials conducted in children - Period 3 - Dupilumab + background therapy - Responders only - Severe Exacerbation to Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of severe exacerbations treated with Office visit in Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of severe exacerbations treated with ED visit in Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of severe exacerbations treated with Hospitalisation in Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiplier applied to Severe Exacerbations, to adjust for population: Child cohort: while using data from trials conducted in children - Background therapy alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Multiplier applied to Severe Exacerbations, to adjust for population: Child cohort: while using data from trials conducted in children - Dupilumab + background therapy - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiplier applied to Severe Exacerbations, to adjust for population: Child cohort: while using data from trials conducted in children - Dupilumab + background therapy - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiplier applied to Severe Exacerbations, to adjust for population: Child cohort: while using data from trials conducted in adults/adolescents - Background therapy alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiplier applied to Severe Exacerbations, to adjust for population: Child cohort: while using data from trials conducted in adults/adolescents - Dupilumab + background therapy - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiplier applied to Severe Exacerbations, to adjust for population: Child cohort: while using data from trials conducted in adults/adolescents - Dupilumab + background therapy - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiplier applied to Moderate Exacerbations, to adjust for population: Child cohort: while using data from trials conducted in children - Background therapy alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiplier applied to Moderate Exacerbations, to adjust for population: Child cohort: while using data from trials conducted in children - Dupilumab + background therapy - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiplier applied to Moderate Exacerbations, to adjust for population: Child cohort: while using data from trials conducted in children - Dupilumab + background therapy - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiplier applied to proportion response, to adjust for population: Child cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of moderate exacerbations - Background therapy alone vs. Dupilumab - Child cohort: while using data from trials conducted in children - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of moderate exacerbations - Omalizumab vs. Dupilumab - Child cohort: while using data from trials conducted in children - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of moderate exacerbations - Mepolizumab vs. Dupilumab - Child cohort: while using data from trials conducted in children - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of severe exacerbations - Background therapy alone vs. Dupilumab - Child cohort: while using data from trials conducted in children - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of severe exacerbations - Omalizumab vs. Dupilumab - Child cohort: while using data from trials conducted in children - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of severe exacerbations - Mepolizumab vs. Dupilumab - Child cohort: while using data from trials conducted in children - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Relative Rate of moderate exacerbations - Omalizumab vs. Dupilumab - Child cohort: while using data from trials conducted in children - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of moderate exacerbations - Mepolizumab vs. Dupilumab - Child cohort: while using data from trials conducted in children - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of severe exacerbations - Omalizumab vs. Dupilumab - Child cohort: while using data from trials conducted in children - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of severe exacerbations - Mepolizumab vs. Dupilumab - Child cohort: while using data from trials conducted in children - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of moving to the 'Uncontrolled asthma' health state - Background therapy alone vs. Dupilumab - Child cohort: while using data from trials conducted in children - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of moving to the 'Uncontrolled asthma' health state - Omalizumab vs. Dupilumab - Child cohort: while using data from trials conducted in children - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of moving to the 'Uncontrolled asthma' health state - Mepolizumab vs. Dupilumab - Child cohort: while using data from trials conducted in children - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of moving to the 'Uncontrolled asthma' health state - Omalizumab vs. Dupilumab - Child cohort: while using data from trials conducted in children - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative Rate of moving to the 'Uncontrolled asthma' health state - Mepolizumab vs. Dupilumab - Child cohort: while using data from trials conducted in children - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative effect of experiencing Severe Exacerbation beyond the trial period (for child trials) for add-on therapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative effect of experiencing Severe Exacerbation beyond the trial period (for child trials) for Background therapy alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with ppFEV1 ≥80% among all patients treated with Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with ppFEV1 ≥80% among all patients treated with Background therapy alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with ppFEV1 ≥80% among all patients treated with Omalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with ppFEV1 ≥80% among all patients treated with Mepolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with ppFEV1 50%-79% among all patients treated with Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with ppFEV1 50%-79% among all patients treated with Background therapy alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with ppFEV1 50%-79% among all patients treated with Omalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with ppFEV1 50%-79% among all patients treated with Mepolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Proportion of patients with ppFEV1 <50% among all patients treated with Dupilumab	
Proportion of patients with ppFEV1 <50% among all patients treated with Background therapy alone	
Proportion of patients with ppFEV1 <50% among all patients treated with Omalizumab	
Proportion of patients with ppFEV1 <50% among all patients treated with Mepolizumab	
Proportion of patients with ppFEV1 ≥80% among responders treated with Dupilumab	
Proportion of patients with ppFEV1 ≥80% among responders treated with Omalizumab	
Proportion of patients with ppFEV1 ≥80% among responders treated with Mepolizumab	
Proportion of patients with ppFEV1 50%-79% among responders treated with Dupilumab	
Proportion of patients with ppFEV1 50%-79% among responders treated with Omalizumab	
Proportion of patients with ppFEV1 50%-79% among responders treated with Mepolizumab	
Proportion of patients with ppFEV1 <50% among responders treated with Dupilumab	
Proportion of patients with ppFEV1 <50% among responders treated with Omalizumab	
Proportion of patients with ppFEV1 <50% among responders treated with Mepolizumab	
Proportion of severe exacerbations requiring Office visit that are fatal - 6-11 years	
Proportion of severe exacerbations requiring Office visit that are fatal - 12-17 years	
Proportion of severe exacerbations requiring Office visit that are fatal - 18-24 years	
Proportion of severe exacerbations requiring Office visit that are fatal - 25-34 years	
Proportion of severe exacerbations requiring Office visit that are fatal - 35-44 years	
Proportion of severe exacerbations requiring Office visit that are fatal - 45-54 years	
Proportion of severe exacerbations requiring Office visit that are fatal - 55-64 years	
Proportion of severe exacerbations requiring Office visit that are fatal - 65-74 years	
Proportion of severe exacerbations requiring Office visit that are fatal - 75-100 years	
Proportion of severe exacerbations requiring ED visit that are fatal - 6-11 years	
Proportion of severe exacerbations requiring ED visit that are fatal - 12-17 years	
Proportion of severe exacerbations requiring ED visit that are fatal - 18-24 years	
Proportion of severe exacerbations requiring ED visit that are fatal - 25-34 years	
Proportion of severe exacerbations requiring ED visit that are fatal - 35-44 years	
Proportion of severe exacerbations requiring ED visit that are fatal - 45-54 years	
Proportion of severe exacerbations requiring ED visit that are fatal - 55-64 years	
Proportion of severe exacerbations requiring ED visit that are fatal - 65-74 years	

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Proportion of severe exacerbations requiring ED visit that are fatal - 75-100 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of severe exacerbations requiring Hospitalisation that are fatal - 6-11 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of severe exacerbations requiring Hospitalisation that are fatal - 12-17 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of severe exacerbations requiring Hospitalisation that are fatal - 18-24 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of severe exacerbations requiring Hospitalisation that are fatal - 25-34 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of severe exacerbations requiring Hospitalisation that are fatal - 35-44 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of severe exacerbations requiring Hospitalisation that are fatal - 45-54 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of severe exacerbations requiring Hospitalisation that are fatal - 55-64 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of severe exacerbations requiring Hospitalisation that are fatal - 65-74 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of severe exacerbations requiring Hospitalisation that are fatal - 75-100 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hazard ratio for other-cause mortality for patients with ppFEV1 50%-79% (versus patients with ppFEV1 ≥80%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hazard ratio for other-cause mortality for patients with ppFEV1 <50% (versus patients with ppFEV1 ≥80%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility in 'No Exacerbation' health state for Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility in 'Controlled Asthma' health state for Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility in 'Uncontrolled Asthma' health state for Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment utility adjustment - Dupilumab + background therapy - Child cohort: while using data from trials conducted in children - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment utility adjustment - Omalizumab + background therapy - Child cohort: while using data from trials conducted in children - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment utility adjustment - Mepolizumab + background therapy - Child cohort: while using data from trials conducted in children - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment utility adjustment - Dupilumab + background therapy - Child cohort: while using data from trials conducted in children - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment utility adjustment - Omalizumab + background therapy - Child cohort: while using data from trials conducted in children - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment utility adjustment - Mepolizumab + background therapy - Child cohort: while using data from trials conducted in children - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Moderate exacerbation-related utility - Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe exacerbation-related utility - exacerbation requiring Office visit - Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe exacerbation-related utility - exacerbation requiring ED visit - Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe exacerbation-related utility - exacerbation requiring Hospitalisation - Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate exacerbation-related utility: duration (in days) for add-on therapies - Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe exacerbation-related utility: duration (in days) for add-on therapies - exacerbation requiring Office visit - Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe exacerbation-related utility: duration (in days) for add-on therapies - exacerbation requiring ED visit - Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe exacerbation-related utility: duration (in days) for add-on therapies - exacerbation requiring Hospitalisation - Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate exacerbation-related utility: duration (in days) for background therapy - Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe exacerbation-related utility: duration (in days) for background therapy - exacerbation requiring Office visit - Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe exacerbation-related utility: duration (in days) for background therapy - exacerbation requiring ED visit - Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe exacerbation-related utility: duration (in days) for background therapy - exacerbation requiring Hospitalisation - Child cohort: while using data from trials conducted in children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caregivers' QoL-related utility adjustment - Dupilumab + background therapy - When the patient is a child (aged 6-<12) - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caregivers' QoL-related utility adjustment - Omalizumab + background therapy - When the patient is a child (aged 6-<12) - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caregivers' QoL-related utility adjustment - Mepolizumab + background therapy - When the patient is a child (aged 6-<12) - All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caregivers' QoL-related utility adjustment - Dupilumab + background therapy - When the patient is a child (aged 6-<12) - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Caregivers' QoL-related utility adjustment - Omalizumab + background therapy - When the patient is a child (aged 6-<12) - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caregivers' QoL-related utility adjustment - Mepolizumab + background therapy - When the patient is a child (aged 6-<12) - Responders only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for healthcare worker's time for Subcutaneous administration: Office visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for healthcare worker's time for Subcutaneous administration: Home visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for healthcare worker's time for Subcutaneous administration: Hospital outpatient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for healthcare worker's time for Intravenous administration: Office visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for healthcare worker's time for Intravenous administration: Home visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for healthcare worker's time for Intravenous administration: Hospital outpatient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
One-off training cost for Subcutaneous self-administration (unit cost)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for Intravenous administration: Hospital day case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost per hour for room costs for Subcutaneous administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost per hour for room costs for Intravenous administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost per hour for equipment costs for Subcutaneous administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost per hour for equipment costs for Intravenous administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for utensil costs for Subcutaneous administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for utensil costs for Intravenous administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of administrations for Dupilumab administered in Office visit setting - External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of administrations for Omalizumab administered in Office visit setting - External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of administrations for Mepolizumab administered in Office visit setting - External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of administrations for Dupilumab administered in Home visit setting - External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of administrations for Omalizumab administered in Home visit setting - External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of administrations for Mepolizumab administered in Home visit setting - External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of administrations for Dupilumab administered in Hospital outpatient setting - External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Proportion of administrations for Omalizumab administered in Hospital outpatient setting - External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of administrations for Mepolizumab administered in Hospital outpatient setting - External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of administrations for Dupilumab that are self-administered - External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of administrations for Omalizumab that are self-administered - External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of administrations for Mepolizumab that are self-administered - External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost per monitoring hour for healthcare worker's time	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for transport for treatment administration: Office visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for transport for treatment administration: Home visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for transport for treatment administration: Hospital outpatient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for transport for treatment administration: Self-administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for hourly wage of patient and/or caregiver	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Outpatient visits: Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Outpatient visits: Pulmonologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Spirometry and FeNo tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Placeholder 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Placeholder 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Placeholder 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Placeholder 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'No Exacerbation' health state - External source of data in Children - Outpatient visits: Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'No Exacerbation' health state - External source of data in Children - Outpatient visits: Pulmonologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'No Exacerbation' health state - External source of data in Children - Spirometry and FeNo tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'No Exacerbation' health state - External source of data in Children - Placeholder 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Resource use per cycle in the 'No Exacerbation' health state - External source of data in Children - Placeholder 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'No Exacerbation' health state - External source of data in Children - Placeholder 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'No Exacerbation' health state - External source of data in Children - Placeholder 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'Controlled Asthma' health state - External source of data in Children - Outpatient visits: Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'Controlled Asthma' health state - External source of data in Children - Outpatient visits: Pulmonologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'Controlled Asthma' health state - External source of data in Children - Spirometry and FeNo tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'Controlled Asthma' health state - External source of data in Children - Placeholder 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'Controlled Asthma' health state - External source of data in Children - Placeholder 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'Controlled Asthma' health state - External source of data in Children - Placeholder 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'Controlled Asthma' health state - External source of data in Children - Placeholder 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'Uncontrolled Asthma' health state - External source of data in Children - Outpatient visits: Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'Uncontrolled Asthma' health state - External source of data in Children - Outpatient visits: Pulmonologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'Uncontrolled Asthma' health state - External source of data in Children - Spirometry and FeNo tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'Uncontrolled Asthma' health state - External source of data in Children - Placeholder 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'Uncontrolled Asthma' health state - External source of data in Children - Placeholder 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle in the 'Uncontrolled Asthma' health state - External source of data in Children - Placeholder 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Resource use per cycle in the 'Uncontrolled Asthma' health state - External source of data in Children - Placeholder 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Outpatient visits: Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Outpatient visits: Pulmonologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Outpatient visits: Psychiatrist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Spirometry and FeNO tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - OCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Emergency room attendance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Ambulance use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost - External source of data in Children - Hospitalisation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for moderate exacerbations - External source of data in Children - Outpatient visits: Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for moderate exacerbations - External source of data in Children - Outpatient visits: Pulmonologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for moderate exacerbations - External source of data in Children - Outpatient visits: Psychiatrist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for moderate exacerbations - External source of data in Children - Spirometry and FeNO tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for moderate exacerbations - External source of data in Children - OCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring Office visit - External source of data in Children - Outpatient visits: Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring Office visit - External source of data in Children - Outpatient visits: Pulmonologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring Office visit - External source of data in Children - Outpatient visits: Psychiatrist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring Office visit - External source of data in Children - Spirometry and FeNO tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring Office visit - External source of data in Children - OCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring ED visit - External source of data in Children - Outpatient visits: Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Resource use per cycle for severe exacerbations requiring ED visit - External source of data in Children - Outpatient visits: Pulmonologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring ED visit - External source of data in Children - Outpatient visits: Psychiatrist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring ED visit - External source of data in Children - Spirometry and FeNO tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring ED visit - External source of data in Children - OCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring ED visit - External source of data in Children - Emergency room attendance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring ED visit - External source of data in Children - Ambulance use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring Hospitalisation - External source of data in Children - Outpatient visits: Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring Hospitalisation - External source of data in Children - Outpatient visits: Pulmonologist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring Hospitalisation - External source of data in Children - Outpatient visits: Psychiatrist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring Hospitalisation - External source of data in Children - Spirometry and FeNO tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring Hospitalisation - External source of data in Children - OCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring Hospitalisation - External source of data in Children - Emergency room attendance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring Hospitalisation - External source of data in Children - Ambulance use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use per cycle for severe exacerbations requiring Hospitalisation - External source of data in Children - Hospitalisation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost per cycle of atopic comorbidities for monoclonal antibodies for the Child cohort - whilst using External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost per cycle of atopic comorbidities for Background therapy alone for the Child cohort - whilst using External source of data in Children	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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N is used to calculate alpha & beta for all parameters that use a beta distribution. N should not be interpreted as a standard error

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Appendix K Omalizumab dosing scheme

Figure 21 Omalizumab Doses (mg per dose) Administered Every Four Weeks by Body Weight and Baseline IgE, Europe

	Body weight (kg)									
Baseline IgE (IU/ml)	≥20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
≥30-100	75	75	75	150	150	150	150	150	300	300
>100-200	150	150	150	300	300	300	300	300	450	600
>200-300	150	150	225	300	300	450	450	450	600	
>300-400	225	225	300	450	450	450	600	600		
>400-500	225	300	450	450	600	600				
>500-600	300	300	450	600	600					
>600-700	300		450	600						
>700-800										
>800-900	ADMINISTRATION EVERY 2 WEEKS SEE TABLE 3									
>900-1000										
>1000-1100										

Appendix L Adult and adolescent population for economic assessment

Main characteristics of included studies

The main characteristics of the studies included in the economic assessment for patients aged ≥12 are presented below. An overview of the main study characteristics is provided in Table 105 and baseline characteristics for each study are summarised in Table 106. As agreed with the Medicines Council, the tables provided resemble the study and baseline characteristics tables in the Medicines Council's background for the treatment guideline for biological treatment of severe asthma for adults and adolescents 12 years and older (104).

QUEST (Castro et al 2018)

QUEST was a randomised, double-blind, placebo-controlled, parallel-group, phase 3 study that assessed the efficacy and safety of dupilumab in patients with uncontrolled moderate-to-severe asthma (105-107).

A total of 1902 patients aged ≥12 years were randomised (2:2:1:1) by use of a centralised treatment allocation system to receive s.c. dupilumab 200 mg Q2W (loading dose 400 mg), 300 mg Q2W (loading dose 600 mg) or 2 matched-volume placebo groups for 52 weeks. Background asthma-controller medicines were continued at a stable dose throughout the trial. Use of LABA, long-acting muscarinic antagonists, antileukotriene agents and methylxanthines was permitted. Throughout the trial, patients were permitted to use a short-acting β2-adrenergic-receptor agonist as necessary for symptom relief.

The study included patients with physician-diagnosed persistent asthma for ≥12 months according to the GINA 2014 guidelines, current treatment with medium-to-high-dose ICS plus up to 2 additional controllers, FEV1 of ≤80% of the predicted normal (or ≤90% of the predicted normal in patients 12-17 years old), FEV1 reversibility of ≥12% and 200 mL; ACQ-5 score of ≥1.5 and a worsening of asthma in the previous year that led to hospitalisation, emergency medical care

or treatment with systemic glucocorticoids for ≥3 days. Patients were recruited irrespective of baseline blood EOS count or levels of biomarkers of type 2 inflammation, e.g. FeNO or IgE. Randomisation was stratified according to age (<18 years or ≥18 years), peripheral-blood EOS count (<300 or ≥300/µL) at screening, ICS dose (medium or high) and by country. Current smokers or former smokers with a smoking history of >10 pack years, and patients with COPD or other lung diseases were excluded.

The primary efficacy outcomes were the annualised rate of severe exacerbation events during the 52-week intervention period and the absolute change from baseline in the FEV1 before bronchodilator use at week 12 in the broad ITT population. A severe asthma exacerbation was defined as a deterioration of asthma leading to treatment for ≥3 days with systemic glucocorticoids or hospitalisation or an emergency department visit leading to treatment with systemic glucocorticoids. Secondary outcomes and pre-specified subgroup analyses included the annualised rate of severe exacerbation events and change from baseline in FEV1 at week 12 in patients with elevated FeNO (≥25ppb), blood EOS count ≥150 cells/µL and ≥300 cells/µL, change from baseline in ACQ-5 score and AQLQ score at week 24, and safety.

Efficacy analyses were performed in the broad ITT population, defined as all the patients who underwent randomisation.

VENTURE (Rabe et al 2018)

VENTURE was a randomised, double-blind, placebo-controlled, parallel-group, phase 3 study that assessed the efficacy and safety of dupilumab in patients with OCS-dependent severe asthma (108, 109).

After an OCS dose-adjustment period of 3-10 weeks, a total of 210 patients were randomised 1:1 by use of a centralized treatment allocation system to receive dupilumab 300 mg Q2W (loading dose 600 mg) or placebo. The 24-week intervention period consisted of a 4-week induction period, during which the adjusted OCS dose was continued; a 16-week period (weeks 4 to 20) during which the OCS dose was adjusted down every 4 weeks according to a protocol prespecified algorithm; and a 4-week maintenance period, during which patients continued the OCS dose that was established at week 20. The adjusted OCS dose was defined as the lowest dose that a patient could receive without having an increase of ≥0.5 (i.e., the minimal clinically relevant difference [MCID]) in the ACQ-5 score, a severe exacerbation or any clinically significant event leading to an upward adjustment in the OCS dose. Background asthma controllers were continued at a stable dose and the use of a short-acting β2-agonist was permitted as needed for asthma symptoms.

The study included patients ≥12 years who had had physician-diagnosed asthma for ≥1 year according to the GINA 2014 guidelines and who had been receiving treatment with regular systemic glucocorticoids in the previous 6 months (5 to 35 mg/ day of prednisone or prednisolone or equivalent). During the 4 weeks before screening, their treatment had to also include a high-dose ICS (fluticasone propionate at a total daily dose of >500 µg or equipotent equivalent) in combination with up to 2 controllers (i.e. a LABA or leukotriene-receptor antagonist) for ≥3 months; FEV1 before bronchodilator use of ≤80% of the predicted normal value (or ≤90% of the predicted normal value in adolescents), FEV1 reversibility of ≥12% and 200 mL, or airway hyperresponsiveness documented in the 12 months before screening. Patients were recruited with no minimum requirements regarding a baseline blood or sputum EOS count or any other type 2 biomarkers. Randomisation was stratified according to the adjusted OCS dose (≤10 mg/day *vs* >10 mg/day of prednisone or prednisolone) and by country. Current smokers or former smokers with a smoking history of >10 pack years, and patients with COPD or other lung diseases were excluded.

The primary efficacy outcome was the % reduction in the OCS dose from baseline to week 24 while asthma control was maintained. Between weeks 20 and 24 asthma control was considered to be maintained if no clinically significant event (based on investigator judgment) leading to an upward adjustment in the OCS dose occurred. For patients who had an exacerbation, the final OCS dose was considered to be 1 step higher than the dose they had been receiving at the time of the exacerbation. Key secondary efficacy endpoints that were assessed in patients with maintained asthma control were the proportion of patients with a reduction from baseline of ≥50% in the OCS dose and the proportion of patients who had a reduction in the OCS dose to ≤5 mg per day. Other endpoints included the proportion of patients who no longer used oral glucocorticoids, the annualised rate of severe exacerbation events (defined as events leading to

hospitalisation, an emergency department visit or treatment for ≥3 days with systemic glucocorticoids at ≥2 times the current dose of OCS) during the 24-week intervention period; the absolute change from baseline in the FEV1 before bronchodilator use at weeks 2, 4, 8, 12, 16, 20, and 24; and the change from baseline in ACQ-5 score and AQLQ score at week 24, and safety. Prespecified subgroup analyses included patients with elevated FeNO (≥25ppb), blood EOS count ≥150 cells/µL and ≥300 cells/µL.

Efficacy analyses were performed in the broad ITT treat population, which included all randomised patients. The safety population included all the patients who received ≥1 dose or a partial dose of dupilumab or placebo, and data were analysed according to the treatment regimen received.

The study characteristics for QUEST and VENTURE are summarized in Table 105.

Table 105 Study characteristics for QUEST and VENTURE

Reference and NCT number	Study design	Follow-up	Age (years)	Relevant outcomes	Asthma diagnosis before or at randomisation documented by	Asthma severity	Refractory asthma (e.g. exacerbations, symptoms, FEV1)	Reduced lung function	EOS (cells/µL)	ICS dose	2nd controller	OCS	# patients randomised per group
Castro 2018 (main) (QUEST) 02414854 *Castro 2019 (lung function)* *Corren 2019b (allergic subgroups)*	Randomised, double-blind, placebo-controlled trial	52 weeks	≥12	Exacerbations FEV1 ACQ-5 AQLQ Symptom score EQ-5D-5L SAE Discontinuations	Airway reversibility (FEV1 ≥12% and 200 mL) *Allergic asthma was defined as total serum IgE ≥30 IU/mL and ≥1 positive perennial aeroallergen-specific IgE value (≥0.35 kU/L) at baseline*[a]	Moderate-to-severe	Asthma worsening in the previous year leading to hospitalisation, emergency medical care or treatment with systemic CS for ≥3 days	FEV1 ≤80% for adults; ≤90% for adolescents	Not inclusion criterion. Randomisation stratified by EOS at screening (≥300 cells/µL, <300 cells/µL)	Medium-to-high (≥500 µg FT or equivalent)	Additional controller drugs required	Not specified	1902 (randomised 2:1, DUP *vs* PBO): DUP 200 mg (N=631), PBO (N=317), DUP 300 mg (N=633), PBO (N=321) all s.c. and Q2W
Rabe 2018 (main) (VENTURE) 02528214 *Rabe 2019 (lung function)*	Randomised, double-blind, placebo-controlled trial	24 weeks	≥12	Exacerbations OCS reduction FEV1 ACQ-5 AQLQ SAE Discontinuations	Airway reversibility (FEV1 ≥12% and 200 mL) or airway hyperresponsiveness (methacholine: PC20 of ≤8 mg/mL)	Severe	Not specified	FEV1 ≤80% for adults; ≤90% for adolescents	Not inclusion or stratification criteria. Subgroup analysis (≥300 cells/µL or <300 cells/µL; ≥150 cells/µL or <150 cells/µL)	High (>500 µg FT or equivalent)	Additional controller drugs required	All OCS dependent (5-35 mg/day prednisone / prednisolone or equivalent)	210: DUP 300 mg (N=103), PBO (N=107) all s.c. and Q2W

References in italics are secondary publications of the primary reference above.

[a] The following perennial allergens were included: *Dermatophagoides farinae, Dermatophagoides pteronyssinus, Alternaria alternata, Cladosporium herbarum*, cat and dog danders, German cockroach, oriental cockroach and *Aspergillus fumigatus*

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CS, corticosteroids; DUP, dupilumab; EOS, blood eosinophils; EQ-5D-5L, European Quality of Life Working Group Health Status Measure

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5 Dimensions, 5 Levels; FEV1, forced expiratory volume in 1 s; FT, fluticasone propionate; ICS, inhaled corticosteroids; IgE, immunoglobulin E; LABA, long-acting beta agonist; OCS, oral corticosteroids; PBO, placebo; PC20, provocative concentration of inhaled methacholine needed to reduce FEV1 by 20%; QoL, quality of life; Q2W, every 2 weeks; Q2W, every 4 weeks; SAE, serious adverse event; s.c., subcutaneously

Table 106 Baseline characteristics for QUEST and VENTURE

Reference	n		Female (%)		Race White (%)		Mean age (years)		# exacerbations in last year		FEV1 (L)		FEV1 % predicted		Mean ACQ score		LABA use* (%)		High dose ICS use (%)		OCS use %, daily dose		FeNO (ppb)		EOS (cells/µL)		IgE (IU/mL)	
	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP	PBO
Castro 2018 (main) (QUEST) ***Castro 2019 (lung function)***	631	317	61	63	Not reported		47.9	48.2	2.1	2.1	1.78	1.76	58.4	58.4	2.8	2.7	LABA or other second controller required		50	54	Not reported		34.5	34.5	349	370	461	394
Corren 2019b (allergic subgroup)	360	183	54	55	Not reported		45.5	44.0	2.0	1.9	1.85	1.84	Not reported		2.7	2.7	LABA or other second controller required		Not reported; medium-to-high-dose inclusion criterion		Not reported		25	27	240	290	304	337
Rabe 2018 (main) (VENTURE) ***Rabe 2019 (lung function)***	103	107	60	61	94	93	51.9	50.7	2.0	2.2	1.53	1.63	51.6	52.7	2.4	2.6	LABA or other second controller required		Inclusion criterion		Inclusion criterion; Dose 10.00 (5.0 to 35.0)[b]		35.6	39.6	370	325	Not reported	

Data are presented for 200 mg dupilumab Q2W *vs* placebo, except for the VENTURE study (300 mg dupilumab Q2W *vs* placebo). References in italics are secondary publications of the primary reference above. Severe asthma was an inclusion criterion for the VENTURE study (Rabe 2018); the proportion of subjects with severe asthma was not reported in the other studies

[a] or equivalent 2nd controller; [b] median (range) in both the dupilumab and placebo groups

ACQ, Asthma Control Questionnaire; DUP, dupilumab; EOS, blood eosinophils; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; IgE; immunoglobulin E; IU, international unit; LABA, long-acting beta agonist; n, number of subjects in the treatment group; OCS, oral corticosteroids; PBO, placebo; ppb, parts per billion; Q2W, every 2 weeks.

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Subgroup populations

Studies in non-OCS dependent asthma and OCS-dependent asthma

The Medicines Council's protocol (110) states that data for the outcomes related to maintenance OCS treatment should be presented for the 300 mg dupilumab dose, while data on all other outcomes should be presented for the 200 mg dose. The 300 mg dose is indicated for patients >12 years with severe asthma treated with OCS, and for patients >12 years with severe asthma and co-morbid atopic dermatitis for which dupilumab is also approved in the EU, including Denmark.

Since patients treated with maintenance OCS can be considered a separate population, it was agreed with the Medicines Council to present the results for the 300 mg dose for all outcomes. This is also deemed relevant since approximately 50% of the Danish patients <18 years could be candidates for treatment with 300 mg dupilumab due to concomitant atopic dermatitis and approximately 10-20% of the Danish adult patients could be candidates for treatment with the 300 mg dose due to maintenance treatment with OCS (110).

Thus, for 2 of the clinical questions (increased EOS population *vs* mepolizumab and increased FeNO population *vs* placebo), where data are available, we present data both for the 200 mg dupilumab dose in a patient population with moderate-to-severe uncontrolled, persistent asthma, and for the 300 mg dupilumab dose in a patient population with severe asthma treated with maintenance OCS.

Dupilumab subgroups covering the protocol-defined populations

The 3 pivotal dupilumab studies had broad eligibility criteria, and patients were not selected for enrolment based on phenotypic traits. Different subgroup analyses of the 3 studies have been performed based on EOS and FeNO levels, which largely cover the 3 patient populations defined in the protocol provided by the Medicines Council. Thus, where available, we used data for the following dupilumab subgroups in this application:

- Increased EOS subgroup to assess the added clinical value of dupilumab *vs* mepolizumab. This subgroup includes patients with baseline blood EOS ≥150 cells/µL.
- Allergic subgroup to assess the added clinical value of dupilumab *vs* omalizumab. This subgroup includes patients with allergy, defined as total serum IgE ≥30 IU/mL and ≥1 positive perennial aeroallergen-specific IgE value (≥0.35 kU/L), and concomitant baseline blood EOS ≥150 cells/µL, or allergy and concomitant FeNO ≥25 ppb at baseline.
- Increased FeNO subgroup to assess the added clinical value of dupilumab *vs* placebo. The protocol provided by the Medicines Council defines this subpopulation as patients with increased FeNO *without* concomitant eosinophilia and *without* concomitant allergy. However, data for this subgroup are not reported. Therefore, available data for patients with elevated baseline FeNO (≥25 ppb) regardless of EOS and allergy status is provided.

Asthma is a heterogeneous disease and most patients are characterised by having more than 1 of several phenotypic traits. Hence, patients with eosinophilic asthma are often also allergic and *vice versa*. This has been confirmed in a recent real-world practice study, including patients from Europe (53). Similarly, patients with elevated FeNO will often possess phenotypic traits of eosinophilic and/or allergic asthma as well. This has also recently been confirmed in another real-world study, including patients from Sweden (52). Only 49 patients in the QUEST study matched the "FeNO only" patient population defined in the protocol, which only includes the patients who are not included in any of the other 2 populations. As data from these 49 patients are not available, and since there is also a significant overlap between the eosinophilic and allergic patient populations defined by current Danish treatment guidelines, we have provided available data for patients with elevated baseline FeNO (≥25 ppb) regardless of EOS and allergy status (Figure 23).

Figure 22 Patient populations in severe asthma

Figure 23: Patient populations in serve asthma

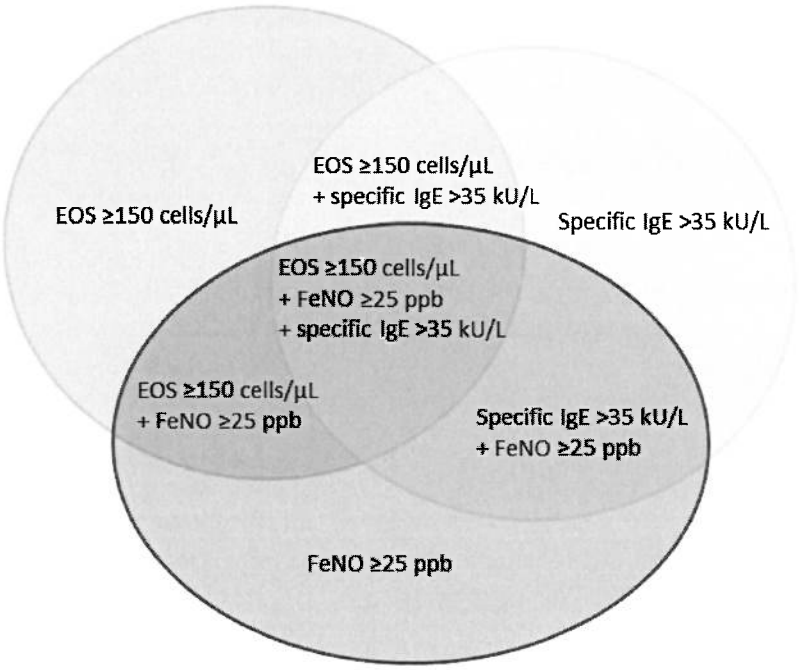


Table 108 provides a summary of the main study characteristics of the 3 dupilumab studies, while Table 110 summarises the subgroups where relevant published data are available. For each of the clinical questions, some outcomes were not available in the specific dupilumab subgroup. In those cases, we provide data for the best alternative population, for example data for the entire allergic population regardless of EOS and FeNO status or, in some cases, data for the ITT population.

Table 107 Overall summary of the dupilumab studies

Table 108: Overall summary of the Dupilumab studies

Dupilumab population	Study	N	Dupilumab dose(s)	Study population	Asthma severity	ICS dose	2nd controller required?	OCS	Age
ITT	QUEST (Castro 2018)	1902 [a]	200 mg Q2W 300 mg Q2W	Uncontrolled, persistent asthma	Moderate-severe	Medium-high	Yes, LABA or other	Not specified	≥12
	VENTURE (Rabe 2018)	210	300 mg Q2W	OCS-dependent asthma	Severe	High	Yes, LABA or other	5-35 mg/day prednisone or equivalent	≥12

[a] includes all doses and dosing frequencies. Only data for the relevant dose and frequency (200 mg Q2W) are used in this application

ICS, inhaled corticosteroids; ITT, intention-to-treat; LABA, long-acting beta agonist; N, number of subjects randomised; OCS, oral corticosteroids; Q2W, every 2 weeks; Q2W, every 4 weeks

Table 109 **Relevant subgroups from the dupilumab studies with available published data**

Table 110 Relevant subgroups from the dupilumab studies with available published data

Dupilumab subgroup	Study	N (% of ITT)	Dupilumab dose relevant for application	EOS level at baseline (cells/µL)	FeNO level at baseline (ppb)	IgE/ allergens
Asthma with type 2-inflammation characterised by eosinophilia						
Increased EOS subgroups	QUEST	669 (35%)	200 mg Q2W	≥150	Any level	Any level
	VEN-TURE	150 (71%)	300 mg Q2W	≥150	Any level	Any level
Asthma characterised by allergy and concomitant eosinophilia or characterised by allergy and concomitant increased FeNO						
Allergic sub-groups	QUEST	384 (20%)	200 mg Q2W	≥150	Any level	Total serum IgE ≥30 IU/mL and ≥1 positive perennial aeroallergen-specific IgE value (≥0.35 kU/L)[a]
		284 (15%)	200 mg Q2W	Any level	≥25	
		543 (29%)	200 mg Q2W	Any level	Any level	
Asthma characterised by increased FeNO						
Increased FeNO sub-groups	QUEST	461 (24%)	200 mg Q2W	Any level	≥25	Any level
	VEN-TURE	114 (54%)	300 mg Q2W	Any level	≥25	Any level

[a] includes the following perennial allergens: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Alternaria alternata*, *Cladosporium herbarum*, cat and dog danders, German cockroach, oriental cockroach and *Aspergillus fumigatus*. Percutaneous allergy skin testing was not performed, and symptoms on relevant exposure for the antigen were not recorded

EOS, blood eosinophils; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; ITT, intention-to-treat; ppb, parts per billion; Q2W, every 2 weeks

Resource use and costs adult/adultescents

Administration costs

The time of administration etc. was the same for adults/adolescent as for children. The DMC estimates that up to 70% of adult/adolescent patients self-administered their treatment, with the remaining 30% assumed to be administered by a healthcare professional in a hospital outpatient setting(62).

Table 111. Resource use associated with drug administration (Adult/Adolescent population)

Treatment	Duration (Minutes per Administration)	% Administered by Healthcare Professional			% self-Administered	
		Office Visit	Home Visit	Hospital Out-patient	%	N
Dupilumab (alone)	10 mins	0.0%	0.0%	30.0%	70.0%	100
Background therapy alone						
Omalizumab (alone)	10 mins	0.0%	0.0%	30.0%	70.0%	100
Mepolizumab (alone)	10 mins	0.0%	0.0%	30.0%	70.0%	100

Monitoring costs

For adults, a 15-minute monitoring period is assumed for the initial administration with no monitoring assumed for subsequent administrations.

Table 112. Monitoring Unit Cost as applied in the model

	Initial Administration Unit Cost	Subsequent Admin-istration Unit Cost	Source
Monitoring by nurse for Adults	DKK 554 per working hour; costed at 15 minutes per hour (= DKK 138.50 per hour)	N/A	Medicinrådet Værdisætning af enhedsomkostninger,vers 1.2

Routine visits and Disease management

Table 113. Routine Care Resource Use per Cycle (4 Weeks) by Level of Control

Resource	In the 'Controlled Asthma' Health State*		In the 'Uncontrolled Asthma' Health State	
	Mean	SE†	Mean	SE†
Adults/adolescents				
Outpatient visits: Nurse	0.333	0.067	0.500	0.100
Outpatient visits: Pulmonologist	0.333	0.067	0.500	0.100
Spirometry and FeNO tests	0.333	0.067	0.500	0.100

Source: For controlled asthma, a monitoring visit every 12 weeks is assumed (20 min nurse, 1 hours physician to do tests, spiro, reversibility, mannitol test, FeNO, blood samples (IgE, eosinophilic status, BAT) / For uncontrolled asthma, a monitoring visit every 8th week is assumed, (20 min nurse, 1 hours physician to do tests, spiro, reversibility, mannitol test, FeNO, blood samples (IgE, eosinophilic status, BAT)

Unit costs for disease management resource use in Denmark were collected from the DMC catalogue of unit costs (79) or other publicly available sources when necessary.

Table 114. Routine Care Unit Costs

Resource	Unit Cost	Source
	Adult/Adolescent population	
Outpatient visits: Nurse	DKK 185.97	Duration of visit: elicited from Danish KOLs via expert in out/validation (20 minutes)
Outpatient visits: Pulmonologist	DKK 1,186.00	www.krl.dk
Spirometry and FeNo tests	DKK 264.75	www.laeger.dk; Performed by a specialist

Appendix M. Relative efficacy of dupilumab versus Omalizumab and Mepolizumab Adult/Adolescent population

In relation to section 8.2.2.4: The adult/adolescent model allowed a comparison versus other biologics including response assessment utilizing numerous assumptions. Two sets of RRs for patients responding to the add-on biologics (1) were incorporated to estimate transition probabilities for patients who respond to other biologics:

- Relative effects as obtained from the ITC (among all patients) versus dupilumab were assumed to apply for responders, implying that although the risk of exacerbations may change in responders, the relative effects for biologics versus dupilumab remain constant regardless of response status.
- Relative effects for responders versus background therapy, as obtained from the reimbursement submissions of each biologic (see Appendix M), were expressed versus dupilumab (2). This approach is consistent with the approach previously adopted in the mepolizumab (64) submissions.

In the base case, the relative effects for responders versus background therapy as obtained from the reimbursement submissions were used. This option was considered most appropriate, given relative effects differ between responders to treatment and the overall patient population, as well as by definition of response. For example, when comparing versus mepolizumab, the definitions of response were inconsistent:

- Mepolizumab: Patients who do not experience a worsening in exacerbation rates are defined as responders
- Dupilumab: Patients who experience a 50% improvement or more in exacerbation rates are considered responders

By definition, even if mepolizumab and dupilumab were equivalent in terms of exacerbation rate reduction, due to the stricter definition adopted for dupilumab, a lower exacerbation rate would be observed among dupilumab responders compared to mepolizumab responders, thereby necessitating alternative relative effects for responders as compared to all patients. The relative effects based on the ITC are used in scenario analysis. However, since that implies an equivalent response definition rule between treatments, the response rate for mepolizumab was lowered in this scenario from 90.9% to 76.7% (Appendix R. Response Rates for Other Monoclonal Antibodies by Population).

Severe Exacerbations

The Table 115 summarises the relative efficacy in reducing severe exacerbations for omalizumab and mepolizumab patients versus dupilumab in the adult/adolescent population of patients outlined in Table 35 without steroid dependency. Data from the Bucher ITCs is used in the base case in the adult/adolescent population.

Table 115. Relative Rates of Experiencing Severe Exacerbations versus Dupilumab – Patients Not on Maintenance OCS

Treatment	Mean	95% Lower	95% Upper
(Adult/Adolescent Population) Bucher Itc[a]			
[redacted]	[redacted]	[redacted]	[redacted]

- [1] These RRs were used post-response assessment, when such an assessment was included in the analysis; they were not used otherwise.
- [2] Relative effects were expressed versus dupilumab for consistency with how relative effects were expressed among all patients and when data from the indirect comparisons were used. Relative effects were expressed versus dupilumab using $\ln RR_{AB} = \ln RR_{AC} - \ln RR_{BC}$ and $SE(\ln RR_{AB}) = \sqrt{[SE(\ln RR_{AC})^2 + SE(\ln RR_{BC})}$.[2]

[redacted]			

Source: a. ITC;(111)

Table 116Table 117 summarises the relative efficacy in reducing severe exacerbations for all biologic responders versus placebo, and the implied relative efficacy versus dupilumab in a population of adult/adolescent patients without steroid dependency.

Table 116. Relative Rates of Experiencing Severe Exacerbations versus Dupilumab – Responders Not on Maintenance OCS (Adult/Adolescent population)

	Dupilumab versus Placebo[a]		Biologic Comparator versus Placebo		Biologic Comparator versus Dupilumab[d]		
	Mean	SE	Mean	SE	Mean	Lower	Upper
[redacted]							
[redacted]							

Source:

a. Estimated based on the number of transitions in each respective population. Rate of exacerbations estimated as the number of transitions to severe exacerbation divided by patient-years, estimated as sum of transitions * years in cycle. Relative rate estimated as ratio of dupilumab rate and placebo rate. Standard error estimated as √(1/a+1/b) where a and b reflect the number of severe exacerbations observed in the placebo and dupilumab arms.

Norman et al. 2013; Page 241, ITT population, INNOVATE(61)

b. Appendix N. Calculations of Relative Risks for Responders to Other Monoclonal Antibodies (Adult/Adolescent Model))
c. Mepolizumab submission to NICE(112) (see Appendix N. Calculations of Relative Risks for Responders to Other Monoclonal Antibodies (Adult/Adolescent Model, based on ITT population in MENSA)
d. Relative effects were expressed versus dupilumab using $lnRR_{AB} = lnRR_{AC} - lnRR_{BC}$ and $SE(lnRR_{AB}) = \sqrt{[SE(lnRR_{AC})^2 + SE(lnRR_{BC})^2}$

For patients on mOCS, relative efficacy estimates from the indirect comparisons were only available versus mepolizumab as outlined in Table 117. Data for responders are provided in Table 118.

Table 117. Relative Rates of Experiencing Severe Exacerbations – All Patients on Maintenance OCS (Adult/Adolescent population)

Treatment	Mean	95% Lower	95% Upper
	Bucher ITC		
Mepolizumab + Background Therapy	[redacted]	[redacted]	[redacted]

Source: ITC;(111)

Table 118. Relative Rates of Experiencing Severe Exacerbations – Responders on Maintenance OCS – Mepolizumab Like population (Adult/Adolescent population)

	Dupilumab versus Placebo[a]		Biologic Comparator versus Placebo		Biologic Comparator versus Dupilumab[b]		
	Mean	**SE**	**Mean**	**SE**	**Mean**	**Lower**	**Upper**
Reduction in OCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reduction in OCS or Exacerbations	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]

Source:

a. Estimated based on the number of transitions in each respective population. Rate of exacerbations estimated as the number of transitions to severe exacerbation divided by patient-years, estimated as sum of transitions * years in cycle. Relative rate estimated as the ratio of dupilumab rate and placebo rate. Standard error estimated as $\sqrt{(1/a+1/b)}$, where a and b reflect the number of severe exacerbations observed in the placebo and dupilumab arms.

Mepolizumab submission to NICE(112)(see

Appendix N. Calculations of Relative Risks for Responders to Other Monoclonal Antibodies (Adult/Adolescent Model), based on ITT population restricted to OCS patients)

Moderate Exacerbations, Uncontrolled Asthma and Lung Function

In addition to the risk of experiencing severe exacerbations, the adult/adolescent model necessitated data on the transition probabilities to moderate exacerbations and uncontrolled asthma, but also the distribution in ppFEV1 in scenario analysis. Informing these inputs for biologic comparators was hampered by limited data and/or data available in an inconsistent format compared to what was required by the model.

Moderate Exacerbations

The risk of experiencing moderate exacerbations was not assessed in the indirect comparisons as this was not collected in mepolizumab trials, and in the case of omalizumab, alternative definitions were used. For example, in the INNOVATE trial, this was defined as a worsening of asthma symptoms requiring systemic CS but not fitting criteria for severe exacerbations,(61) whilst in the Liberty Asthma QUEST trial, this was defined based on a number of criteria Table 119.

Table 119. Comparison of Definitions of Moderate Exacerbations Across Trials

	LIBERTY ASTHMA QUEST(105)	INNOVATE(61)
PEF	A decrease in AM or PM PEF of 30% or more on 2 consecutive days of treatment, based on the defined stability limit	Worsening of asthma symptoms requiring treatment with systemic CS not meeting the definition of clinically severe (PEF/FEV_1 < 60% of personal best, requiring systemic CS] resulting in hospitalisation or ER treatment, in the past 12 months)
Rescue Medication	≥ 6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24-hour period (compared to baseline) on 2 consecutive days	
Nighttime Awakenings	NA	
Symptoms	NA	
Lung Function	≥ 20% decrease in pre-bronchodilator FEV_1 compared with baseline	
ICS Dose	Increase in ICS dose ≥ 4 times than the dose at Visit 2	

Due to the inconsistent definitions adopted, any analyses comparing moderate exacerbation risks between biologics would be subject to bias. Therefore, in the base case in the adult/adolescent model, it was assumed that the moderate exacerbation risk would be equivalent across biologic treatments. A RR of 1 was therefore implemented, which was varied by 20% in sensitivity analyses to determine the influence of this assumption.

Assuming relative efficacy would be unaffected by the inconsistent definitions, RRs of experiencing moderate exacerbations were derived, which were examined as an exploratory scenario in the adult/adolescent model Table 120.

Table 120. Relative Rates of Experiencing Moderate Exacerbations – Exploratory Analyses (Adults/Adolescents)

Comparator	Biologic vs Placebo	Dupilumab vs Placebo[b]	Biologic vs Dupilumab[c]
All Patients			
Omalizumab	[redacted]	[redacted]	[redacted]
Responders			
Omalizumab	[redacted]	[redacted]	[redacted]

Source:

a. Norman et al. 2013; Table 66, INNOVATE: all(61)

b. Estimated based on the number of transitions in each respective population. Rate of exacerbations estimated as the number of transitions to severe exacerbation divided by patient-years, estimated as the sum of transitions * years in cycle. Relative rate estimated as ratio of dupilumab rate and placebo rate. Standard error estimated as √(1/a+1/b), where a and b reflect the number of severe exacerbations observed in the placebo and dupilumab arms.

c. Relative effects were expressed versus dupilumab using $\ln RR_{AB} = \ln RR_{AC} - \ln RR_{BC}$ and $SE(\ln RR_{AB}) = \sqrt{[SE(\ln RR_{AC})^2 + SE(\ln RR_{BC})^2}$

Lung Function

Although mean change in FEV1 in litres was available from the indirect comparison, the distribution of patients across ppFEV1 categories was assumed to be equal across biologics in the adult/adolescent model. To transform the mean change in FEV1 in litres to ppFEV1, several assumptions would have been needed. As the indirect comparisons indicated that FEV1 results were favourable for dupilumab, this assumption was considered conservative.

OCS Reduction

Relative effects, expressed as odds ratios (ORs) in terms of OCS reduction, were only available versus mepolizumab. The following outcomes were available versus mepolizumab:

- Reduction in OCS dose < 5 mg/day (OR)
- Reduction in OCS dose = 50% (OR)

Reduction in the daily OCS dose to a dose < 5 mg/day was available for both treatments. Withdrawal from OCS (i.e., 100% reduction) was available versus mepolizumab. These ORs (Table 121) are used to estimate the proportion of adult/adolescent patients achieving a daily dose < 5 mg and those withdrawing from treatment with mepolizumab. In the absence of information to inform withdrawal among responders, it is assumed that the ORs of withdrawing from treatment were consistent among all adult/adolescent patients and responders.

Table 121. Odds Ratios – OCS Reduction (Adult/Adolescent population)

	Withdrawal from OCS			Reduction to a Daily Dose < 5mg		
Treatment	**Mean**	**95% Lower**	**95% Upper**	**Mean**	**95% Lower**	**95% Upper**
			ITC[a]			
Mepolizumab + Background Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: a. ITC;(111)

Proportion of Patients Achieving Response

The definitions of response and timings of response assessment used for each of the biologics in the adult/adolescent model are summarised in Table 122 for patients not on mOCS and in Table 123 for patients on mOCS. As

highlighted above, these data reflect the proportions of patients achieving response among a population of patients examined in the respective pivotal trial of each comparator. In addition to the proportion of responders being based on alternative populations, they are based on alternative definitions of response; therefore, the data are not comparable. Appropriate caution is recommended when comparing against other biologics under a response assessment scenario. Data on proportion of responders were not reported for placebo, thus, comparisons between treatments are based on a naïve comparison.

The proportions of patients achieving response in more restricted (or reimbursed) populations are provided in Appendix R. Response Rates for Other Monoclonal Antibodies by Population (where reported).

Table 122. Response Assessment for Other Monoclonal Antibodies in Adult/Adolescent Model: Criteria, Timing and Proportions of Responders – Patients not on mOCS

Treatment	Response Definition	Review Timing (Weeks from First Administration)	% Responders	
			Mean	n
Omalizumab[a]	Physician's GETE	16 weeks	56.5%	118*
Mepolizumab[b]	improvement or stable exacerbation rates	52 weeks	90.9%	350

* Calculated using the number of patients in the omalizumab arm of the INNOVATE trial (209 patients).

a. Norman et al. 2013, Table 7;[61] based on ITT population from the INNOVATE trial

b. NICE TA479, Reslizumab – company evidence submission, Table 105 (page 190);(114) based on adult patients at GINA Step 4/5 with ≥ 2 exacerbations in the preceding year from the 3082 and 3083 studies

c. NICE TA431, Mepolizumab – company evidence submission, Table 104 (page 197);(112) based on ITT population from MENSA trial

Table 123. Response Assessment for Other Monoclonal Antibodies in Adult/Adolescent Model: Criteria, Timing and Proportions of Responders – Patients on mOCS

Treatment	Response Definition	Review Timing (Weeks from First Administration)	% Responders	
			Mean	n
Mepolizumab	Reduction in exacerbations	52 weeks	83.0%	83

* Calculated using the number of patients in the omalizumab arm of the INNOVATE trial (209 patients).

Source: NICE TA431, Mepolizumab – company response to appraisal consultation document (ACD),(66) Appendix 2, based on ITT population from MENSA trial restricted to maintenance OCS patients

Table 124. Response Assessment for Other Monoclonal Antibodies in Adult/Adolescent Model: Criteria, Timing and Proportions of Responders – Patients not on mOCS

Treatment	Response Definition	Review Timing (Weeks from First Administration)	% Responders	
			Mean	n
Omalizumab[a]	Physician's GETE	16 weeks	56.5%	118*
Mepolizumab[b]	Improvement or stable exacerbation rates	52 weeks	90.9%	350

* Calculated using the number of patients in the omalizumab arm of the INNOVATE trial (209 patients).

† Assumed based on the number of patients in the 3082 and 3083 studies (i.e., 477 patients in reslizumab arms).

Source:

a. Norman et al. 2013, Table 7;[61] based on ITT population from the INNOVATE trial

b. NICE TA431, Mepolizumab – company evidence submission, Table 104 (page 197);(112) based on ITT population from MENSA trial

Safety and Mortality Inputs

OCS-related Adverse Events

As risks of experiencing AEs were only applied to those who were steroid dependent, and OCS was not considered for the child population, AEs were only applicable to adult/adolescent patients. Alternative risks were applied to the proportion of patients requiring OCS treatment (i.e., those who did not withdraw completely as compared to those who did withdraw), based on the average OCS dose, assuming the risk of experiencing OCS-related AEs is constant over time.

AEs modelled in the adult/adolescent model were retained. Those were selected based on the availability of data.(115) The model considered the following AEs:

- Bone-related conditions
- Infections: severe infections, herpes zoster
- Metabolic disorders: hypertension, diabetes mellitus
- Ocular disorders: cataracts, glaucoma
- Gastrointestinal disorders: peptic ulcer
- Renal disorders: chronic kidney disease
- Psychiatric disorders: affective disorders
- Cardiovascular events

An overview of studies from the UK (as well as from the US) assessing the relationship between mOCS use and AEs in patients with asthma is provided in Appendix S. OCS-related Adverse Events – Sources Evaluated (for Adult/Adolescent Model). Most identified studies reported relative effects of experiencing AEs depending on OCS dose, OCS use or number of prescriptions. A systematic review of OCS-related AEs in the US and UK by Manson et al. (2009) was also identified.(116) That review identified several studies; however, these were not restricted to an asthmatic population and may be outdated.

A recently published CPRD study by Bloechliger et al. (2018) estimated the incidence rates of potential CS-related AEs in large cohorts (N's = 165,900 to 269,368) of patients with asthma.(117) This study represents one of the largest studies conducted to date investigating OCS-related AEs in an asthmatic population and it is recommended that the incidence rates of experiencing OCS-related AEs be informed based on this study in the base case. This includes the AE incidence rates among patients not receiving OCS (the "baseline risk" of AE; see Table 125) as well as the relative risks of experiencing AEs in patients receiving different doses of OCS as compared to not receiving OCS; Bloechliger et al. (2018) reported odds ratios for OCS use versus no OCS use (**Table 126**) for three different levels of OCS doses: ≤ 1 mg/day; > 1 – ≤ 5 mg/day; > 5 mg/day.(117)

Data based on an analysis of CPRD data conducted by GlaxoSmithKline (GSK) as part of the mepolizumab submission to NICE were also considered to inform the risk of OCS-related AEs.(64) The study by Bloechliger and colleagues was published in April 2018 and until then the GSK study seemed to represent the only study in asthmatic patients reporting incidence of AEs. However, limited details on the methods used were provided in the mepolizumab submission, and it received criticism regarding the fact that the relative risk of an event may not be linear in terms of magnitude of the dose of OCS (as GSK estimated relative risks of AEs due to additional gram of average cumulative OCS dose [per 28-day period] versus no OCS use). Due to the limitations associated with the GSK analyses, the study by Bloechliger et al. was considered more representative and used in the adult/adolescent model for dupilumab. Existence of Denmark-specific data on the frequency of AEs related to mOCS use was explored. However, as no appropriate data was identified, the UK data by Bloechliger et al. was used after confirming these data appear appropriate with Danish KOLs.

Table 125. Risk of Experiencing AEs in Patients Not Receiving OCS (UK Model)

	Incidence Rate per 100 Person-Years, Not on OCS	
AE	**Mean**	**SE**
Bone-related Conditions	1.21	0.02
Severe Infections	1.78	0.02
Herpes Zoster	0.47	0.01
Hypertension	1.19	0.02
Diabetes Mellitus	0.58	0.01
Glaucoma	0.17	0.01
Cataracts	0.59	0.01
Peptic Ulcer	0.09	0.00
Chronic Kidney Disease	0.98	0.01
Affective Disorders	0.89	0.01
Cardiovascular Events	0.47	0.01

Source: Calculated from Bloechliger et al. 2018, Table 3.(115) Incidence rates were divided by 10 to obtain values per 100 person-years and SEs were calculated based on the 95% CIs provided in the source, assuming a Normal distribution.

Table 126. ORs of Experiencing OCS-related AEs by Average Daily Dose of OCS versus No OCS Use (UK Model)

	OR of AE for Low-dose (≤ 1 mg/d) OCS vs No OCS Use			OR of AE for Medium-dose (> 1–≤ 5 mg/d) OCS vs No OCS Use			OR of AE for High-dose (> 5 mg/d) OCS vs No OCS Use		
AE	**Mean**	**95% CI Lower Limit**	**95% CI Lower Limit**	**Mean**	**95% CI Lower Limit**	**95% CI Lower Limit**	**Mean**	**95% CI Lower Limit**	**95% CI Lower Limit**
Bone-related Conditions	1.244	1.179	1.333	1.385	1.192	1.667	1.500	1.013	2.396
Severe Infections	1.985	1.924	2.061	3.036	2.670	3.251	2.433	1.773	3.258
Herpes Zoster	1.308	1.192	1.449	1.526	1.269	1.924	0.969	0.492	1.955
Hypertension	1.038	0.953	1.179	1.026	0.875	1.244	1.128	0.727	1.833
Diabetes Mellitus	1.308	1.205	1.436	1.538	1.308	1.955	1.621	0.914	2.944
Glaucoma	1.083	0.847	1.346	0.992	0.653	1.526	1.076	0.282	4.656
Cataracts	0.938	0.867	1.090	1.179	0.961	1.410	3.425	2.287	5.090
Peptic Ulcer	1.397	1.064	1.909	1.652	0.945	2.830	1.652*	0.945*	2.830*
Chronic Kidney Disease	1.167	1.077	1.282	1.128	0.969	1.346	1.621	1.077	2.440
Affective Disorders	1.423	1.308	1.667	1.636	1.231	1.985	2.803	1.591	5.050
Cardiovascular Events	1.321	1.192	1.462	1.462	1.179	1.879	0.953	0.435	2.248

Source: Bloechliger et al. 2018, Figure 2(115) The forest plot was imported into the Engauge Digitizer software (version 4.1). Since the horizontal scale varies across the plot (one can see for instance that the space between 0.2 and 0.5 is a lot larger than the space between 5 and 6), the data points had to be extracted in waves, with the axes reset after each wave. This was done as follows: 1) We began by identifying the points that fell between the x-axis values of 0.2 and 0.5 (the first interval on the plot). 2) We indicated to the digitizer tool where the points with the coordinates (0.2,0), (0.5,0) and (0.5,1) were located in the imported plot, and then we extracted those points with x-axis values between 0.2 and 0.5 and saved those values. 3) Next, we identified which points fell between 0.5 and 1 on the x-axis and we reset the digitization so that (0.5,0), (1,0) and (1,1) were being used to define the image scale. 4) Then we extracted those points that fell between the x-axis values of 0.5 and 1. This process was conducted six more times to extract the values that fell in the following ranges with regards to the x-axis: 1–1.5; 1.5–2; 2–3; 3–4; 4–5; 5–6. Once this was completed, all extracted data points with the same y-axis value were collated in order to be able to determine the mean OR and the limits of the CI of the OR for each AE and each OCS dose category (each corresponding to a different level on the y-axis).

* Assumed same as for the > 1–≤ 5mg/d category. No OR was reported by Bloechliger et al. 2018 for peptic ulcer for the > 5 mg/d category due to the very small number of patients involved.(115)

Fatality Rate Associated with Exacerbations Leading to Hospitalisation

As no additional data had been identified since the last severe asthma NICE technology appraisal during which asthma-related mortality was examined at length, the preferred committee assumption for that appraisal (benralizumab TA565)(65) was used in the base case in the final UK adult/adolescent model for dupilumab. These data, accepted by the committee and ERG in the NICE assessment of benralizumab, reflected the most conservative estimates used across models for asthma to date. They were based on data from Watson et al. (2007) (67), age-adjusted based on Roberts et al. (2013)(68), with further adjustment based on the most recent BTS

audit.(118) As no Danish data was identified regarding mortality related to asthma exacerbations, the same UK data is used in the Danish base case. Danish KOLs validated this approach.

In the benralizumab submission to NICE, fatality rates following a hospitalisation for severe exacerbation among the 45+ age group in the Watson et al. 2007 study (67) were adjusted based on the study by Roberts et al. 2013 (68). This adjustment was conducted as use of data by Watson has previously been criticised due to limited differentiation in mortality between patients aged 45-100. The exact calculation approach was not detailed in the submission; however, it is presumed that the odds ratios for the age groups 45–54, 55–64 and 65+ and the age distribution observed in the Roberts study were used to derive fatality rates within the 45+ group, whilst maintaining the average risk observed in the Watson study.

Mortality estimates were further adjusted thereafter for all age groups with the exception of patients aged 65+ years to align with the most recent estimates of mortality in the UK (119). Following the manufacturer's original submission, the ERG indeed criticised the mortality estimates used; specifically, these were considered to be unrepresentative based on recent evidence from the BTS asthma audit. The BTS audit conducted in 2016 reported that there were 33 deaths among 4,258 admissions of adult patients with asthma, corresponding to an average death rate of 0.0078 per hospital admission.(118) This average death rate per hospital admission implied by the combination of the Watson and Roberts studies was 0.01943, reflecting a 2.5 increase.(65) Fatality rates for all age groups (apart from 65+ years) were therefore divided by a factor of 2.5 by the ERG. The revised estimates (Table 40) were subsequently accepted by the NICE committee and were also used in the base case in the model for dupilumab.

Though data utilised in the benralizumab submission reflect the most conservative estimates used to date, fatality rates by age among patients aged 45+ years were deduced based on multiple sources. An updated analysis of the Camper Health Knowledge Systems (CHKS) database (similar to the Watson et al. study), including more granular age bands, was conducted in 2016 (120), including observations between 2000 and 2015. The average death rate among adults based on this updated analysis was 1.12% (see Appendix P for observed data), reflecting a 1.4 increase as compared to the BTS audit data (119). As the audit indicated that mortality rates remained stable among patients aged 75+ years, case fatality rates were adjusted by a factor of 1.6905 among patients aged 18–65 years to obtain an average rate of 0.78%. Use of these alternative estimates were examined in scenario analyses in the adult/adolescent model (Table 40). As the BTS asthma audit did not provide data for children nor adolescents(119) and in alignment with the approach described above with the base-case source (data from Watson et al. combined with Roberts et al., for which the same adjustment by 2.5 was applied for children and adolescents as was applied for adults), the same adjustment as for adults (i.e., by a factor of 1.6905) was applied to the CHKS data for patients aged 0–11 and 12–16 in order to derive the estimates used in this scenario analysis for children aged 6–11 and adolescents aged 12–17, respectively.

Adjustment of Other-cause Mortality based on Lung Function

In the adult/adolescent model, in the scenario where other-cause mortality was adjusted based on lung function, HRs of other-cause mortality by lung function level were based on a study conducted by Sanofi/Regeneron. Analyses were conducted to identify the influence of lung function on other-cause mortality (i.e., excluding death due to severe exacerbations) using the CPRD database (121). These analyses evaluated the influence of lung function on mortality, excluding death due to asthma, in patients hospitalised for asthma. A Cox proportional hazard model was fitted with moderate-severe asthma, aged 18 years or older, adjusted for age at index, smoking, body mass index (BMI), gender, rhinitis, chronic sinusitis, nasal polyps, atopic dermatitis, diabetes, anaphylaxis, ischaemic heart disease, heart failure, food allergy, anxiety, depression and psoriasis. HRs were obtained for the following three categories of ppFEV1: ppFEV1 ≥ 80% (reference category), ppFEV1 between 50% and 79%, and ppFEV1 < 50% (Table 127).

Table 127. HRs for Other-cause Mortality by ppFEV$_1$ Level

ppFEV$_1$ Level	Hazard Ratio		
	Mean	**95% CI Lower Limit**	**95% CI Upper Limit**
≥ 80%	1.000		
50%–79%	1.862	1.606	2.159
< 50%	2.919	2.468	3.452

Source: CPRD analysis, Sanofi/Regeneron data on file(121)

Based on these distributions and on the HRs associated with the different levels of ppFEV1, HRs were calculated for each treatment (as a weighted average of the proportions of patients in each ppFEV1 category and of the HRs corresponding to each category) compared to a cohort of patients with ppFEV1 ≥ 80% (Table 128).

Table 128. HRs of Other-cause Mortality by Treatment as Compared to a Cohort of Patients with ppFEV$_1$ ≥ 80%

	LIBERTY ASTHMA QUEST – EMA Population	LIBERTY ASTHMA VENTURE – EMA Population
Dupilumab + Background Therapy (All Patients)	1.819	1.941
Responders – Based on Improvement in Exacerbation Risk	1.765	1.911
Responders – Based on Decrease in OCS Dose	NA	1.863
Background Therapy Alone	1.031	2.202

* Example calculation: 23.35% x 1.000 + 61.68% x 1.862 + 14.79% x 2.919 = 1.819

Data presented in Table 128 were then expressed versus the general population using assumptions. As described in Appendix P. Implementation of Impact of Lung Function on Other-cause Death in Adult/Adolescent Model, three different approaches to this normalisation were included in the adult/adolescent model:

1. Assume other-cause mortality risk in patients treated with background therapy is equivalent to the general population
2. Assume other-cause mortality risk in patients treated with the monoclonal antibody associated with the largest improvements in FEV$_1$ is equivalent to the general population
3. Consider ppFEV$_1$ data for the general population and estimate HR versus general population

The HRs obtained (for all patients and for responders) with these different approaches are summarised in Table 129. These normalised HRs were then applied to the other-cause mortality rates observed in the general population for each respective treatment.

We considered that the most appropriate approach to derive excess mortality versus the general population would involve considering the distribution of ppFEV1 in the general population (the third option); however, this option is hampered by data availability. Generally, studies evaluating lung function focus on patients with respiratory diseases; thus, limited data—if any—were identified to inform these inputs based on a pure general population. Nonetheless, to determine the potential influence of using data from a general population, the distribution of the UK general population in terms of ppFEV1 was estimated based on an older Danish study by Lange and colleagues (1998) (as presented in Table 130 (122). Given the data were outdated, do not reflect a UK population and were based on a population without lung disease, all assumptions were examined in scenario analysis in the adult/adolescent model.

Table 129. Normalised HRs of Other-cause Mortality by Treatment – Expressed versus UK Adult/Adolescent Population

	LIBERTY ASTHMA QUEST – EMA Population	LIBERTY ASTHMA VENTURE – EMA Population
Assume Other-cause Mortality Risk in Patients Treated with Background Therapy is Equivalent to the General Population		
Dupilumab + Background Therapy (All Patients)	0.925	0.882
Responders – Exacerbation Reduction	0.897	0.868
Background Therapy Alone	1.000	1.000
Assume Other-cause Mortality Risk in Patients Treated with the Monoclonal Antibody Associated with the Largest Improvements in FEV_1 Is Equivalent to the General Population*		
Dupilumab + Background Therapy (All Patients)	1.031	1.016
Responders – Exacerbation Reduction	1.000	1.000
Background Therapy Alone	1.114	1.152
Include $Ppfev_1$ Data for the General Population and Estimate HR Versus General Population		
Dupilumab + Background Therapy (All Patients)	1.488**	1.588
Responders – Exacerbation Reduction	1.444	1.564
Background Therapy Alone	1.609	1.802

* Note that in the model, only one response rule is considered at a time; therefore, the normalised HR estimated in this scenario would vary based on the response definition selected.
** Example calculation: 1.819 (Table 128) / 1.222 (see footnote underneath Table 130) = 1.488

Table 130. Distribution of $ppFEV_1$ in the Adult/Adolescent Population

$ppFEV_1$ Level	General Population
≥ 80%	75.68%
50%–79%	23.14%
< 50%	1.182%

Source: Calculated from Lange et al. 1998;(122) data for patients without asthma; HR of the general population versus a cohort of patients with $ppFEV_1 \geq 80\%$ would be 75.68% x 1.000 + 23.14% x 1.862 + 1.182% x 2.919 = 1.222

Appendix N. Calculations of Relative Risks for Responders to Other Monoclonal Antibodies (Adult/Adolescent Model)

Mepolizumab Responders

The model used in the mepolizumab submission to NICE included three types of clinically significant exacerbations: exacerbations requiring treatment with OCS, exacerbations requiring an ER visit, and exacerbations requiring hospitalisation.(112) That model used a single event rate for all clinically significant exacerbations and then used the respective proportions of the three different types (based on trial data) to distribute the exacerbations by type. Table 131 below summarises the various RRs (in terms of clinically significant exacerbation rates) for mepolizumab responders versus SoC, corresponding to the populations explored in the submission. The following section describes the rationale and the methods used to derive these estimates of relative efficacy. For our model, it was assumed that rates of clinically significant exacerbations would be applicable to severe exacerbations in the model.

The following three populations were included in the submission of mepolizumab to NICE (see Table 99 in the company evidence submission(112)):

1. **"Mepolizumab modified ITT population":** ITT population (defined by the inclusion criteria of the MENSA trial). Patients have a blood eosinophil count ≥ 150 cells/µL at initiation of treatment or a blood eosinophil count ≥ 300 cells/µL in the prior 12 months, who experience ≥ 2 exacerbations in the previous year. This population was used in the company's base-case analysis and in the comparison against omalizumab. This population was used in our base-case analysis for the "Mepolizumab-like population".

2. **"Mepolizumab company proposed population": Patients who have a blood eosinophil count of ≥ 150 cells/µL at initiation of treatment; and ≥ 4 exacerbations in the previous year or dependency on maintenance OCS.**

3. **"Mepolizumab company proposed population excluding OCS users with < 4 exacerbations in the previous year": Patients have a blood eosinophil count ≥ 150 cells/µL at initiation of treatment; and ≥ 4 exacerbations in the previous year.**

In addition, in the response to the appraisal consultation document data were provided for the ITT population restricted to maintenance OCS, used for comparisons versus steroid dependent populations.

The mean annual exacerbation rates (and SEs) for SoC and for mepolizumab responders for these three populations were reported in Table 126 in the company evidence submission(112) and are included in the first three rows of Table 131 below.

Table 131. Relative Risk of Clinically Significant Exacerbations for Mepolizumab Responders versus SoC based on the NICE Appraisal of Mepolizumab

Comparator	SoC—Annual Rate (SE)	Mepolizumab, Post-continuation Assessment—Annual Rate (SE)	Relative Rate (SE)
Mepolizumab (modified ITT population)	1.7439 (0.09773)*	0.5504 (0.1459)*	0.316 (0.271)
Mepolizumab (company proposed population)	2.65 (0.157)*	0.6447 (0.2238)*	0.243 (0.352)
Mepolizumab (company proposed population excluding OCS users with < 4 exacerbations in the previous year)	3.1005 (0.1795)*	0.7232 (0.2316)*	0.233 (0.325)
Mepolizumab (ITT restricted to maintenance OCS)	2.120 (0.109)**	0.990 (0.215)	0.467(0.150)

Sources:

* Table 126 in the company evidence submission (112). ** Appendix 2 in company response to appraisal consultation document; SEs were not reported, however, approximated based on N=83 responders in the mepolizumab responders and assuming N=46 based on 191 patients randomised to placebo in MENSA and 24% of patients receiving maintenance OCS. Number of events approximated by multiplying rate times number of patients in each arm.

Relative Rates

Mean RRs for the three populations were calculated by dividing the annual rate of exacerbation for mepolizumab responders by the annual rate of exacerbation for patients on SoC. CIs for these mean RRs were calculated using the following formula:

$$95\%\ CI = e^{\left(\ln(RR) \pm z_{0.975}\sqrt{\frac{1}{a}+\frac{1}{b}}\right)}$$

where $RR$is the mean relative rate, $z_{0.975}$ is the z-score for the 97.5th percentile of the standard normal distribution (≈ 1.96), a is the number of exacerbation events that patients randomised to SoC experienced and b is the number of exacerbation events that mepolizumab responders experienced. a (and similarly, for b) is calculated by the following formula:

$$a = \left(\frac{r}{SE(r)}\right)^2$$

where r is the mean exacerbation rate and $SE(r)$ is the SE of the mean exacerbation rate. The text below provides further explanations about this formula.

This formula assumes that the number of exacerbations (noted D below) during a period follows a Poisson distribution, which is equivalent to assuming that the time to event is constant (time to exacerbation is assumed to be exponentially distributed). A limitation of this assumption is that it does not consider the change in exacerbation risk given a patient had an exacerbation. Writing the likelihood $P(D)$ of the number of events D, we have:

$$P(D) = \frac{(rT)^D e^{-rT}}{D!}$$

where r is the event rate per patient-year of exposure and T is the number of patient-years of exposure. Writing the log-likelihood ll, we have:

$$ll = Dln(rT) - rT - \ln(D!)$$

Taking the derivative of the log-likelihood with respect to r and setting it equal to zero to maximise the log-likelihood, we have:

$$\frac{\delta ll}{\delta r} = \frac{D}{r} - T = 0$$

The maximum likelihood estimate for the expected value of r is then:

$$E[r] = \frac{D}{T}$$

The variance of the mean estimate is then:

$$Var[E[r]] = Var\left[\frac{D}{T}\right] = \frac{1}{T^2}Var[D] = \frac{1}{T^2}E[D] = \frac{rT}{T^2} = \frac{r}{T}$$

since the mean and the variance of Poisson-distributed random variables are the same (= rT). r is estimated as $\frac{D}{T}$, therefore the standard error of r can be written as:

$$SE(r) = \frac{\sqrt{D}}{T}.$$

Given the mean and SE of r, we can use $D = \frac{r^2}{SE(r)^2}$ to get the number of events, which we can then use in the formula for calculation of the CI of the RR.

Appendix O. Estimation of Transition Probabilities

The transition probabilities in the adult/adolescent model were estimated in the form of a transition probability matrix P (or transition matrix), whose elements Pij-s represent the estimated probabilities from transitioning from state i to state j, where i and j are members of the given set of health states. As an illustration, the transition matrix of the five-sub-state model is depicted in Table 132 where the starting states are presented by different rows and states of transitions are presented by different columns. Probabilities in each row must add up to one. Transitions are allowed from any state to any state.

Table 132. Five-Sub-State Transition Probability Matrix

From (*i*) / To (*j*)	Uncontrolled Asthma	Controlled Asthma	Moderate Exacerbation	Severe Exacerbation	Sum
Uncontrolled Asthma	$P_{1,1}$	$P_{1,2}$	$P_{1,3}$	$P_{1,4}$	$\sum P_{1,j}=1$
Controlled Asthma	$P_{2,1}$	$P_{2,2}$	$P_{2,3}$	$P_{2,4}$	$\sum P_{2,j}=1$
Moderate Exacerbation	$P_{3,1}$	$P_{3,1}$	$P_{3,3}$	$P_{4,2}$	$\sum P_{3,j}=1$
Severe Exacerbation	$P_{4,1}$	$P_{4,2}$	$P_{4,3}$	$P_{4,4}$	$\sum P_{4,j}=1$

Estimating Transition Probabilities

As the model cycle's length was four weeks, all transition probability matrices were calculated for four weekly transitions. The transition probability estimation involves counting the number of patients in each health state across the relevant time periods, along with the frequency of transitions to other health states from that health state across the same time periods.

To estimate transition probabilities of a given subgroup, all transitions between health states (observed or imputed) were counted during a given period. Four-week jumps were collected to a transition frequency matrix (for an illustration, see Table 133).

Table 133. Five-Sub-State Transition Frequency Matrix

From (*i*) / To (*j*)	Uncontrolled Asthma	Controlled Asthma	Moderate Exacerbation	Severe Exacerbation	Sum
Uncontrolled Asthma	$N_{1,1}$	$N_{1,2}$	$N_{1,3}$	$N_{1,4}$	$\sum N_{1,j}= N_1$
Controlled Asthma	$N_{2,1}$	$N_{2,2}$	$N_{2,3}$	$N_{2,4}$	$\sum N_{2,j}= N_2$
Moderate Exacerbation	$N_{3,1}$	$N_{3,1}$	$N_{3,3}$	$N_{4,2}$	$\sum N_{3,j}= N_3$
Severe Exacerbation	$N_{4,1}$	$N_{4,2}$	$N_{4,3}$	$N_{4,4}$	$\sum N_{4,j}= N_4$

The maximum likelihood estimate of the transition probability matrix is the matrix of relative frequencies. Namely, the counts of transitions (Ni,j) in each row (for any i) are divided by the total sum of transitions $\sum$ Ni,j= Ni in that row (row i). Transition probabilities are estimated as Pi,j=Ni,j/Ni for any i,j=1,...,4. The total number of transitions in each row (Ni) is provided along with the estimated probabilities (Pi,j) for all matrices that are estimated.

Transition probabilities were calculated from transitions of patients while they were on randomised treatment (i.e., transitions of patients after they permanently discontinue the randomised treatment were not included in the calculation of the number of transitions).

A similar approach to estimating transition probabilities was applied for the children data from the LIBERTY ASTHMA VOYAGE trial.

Appendix P. Implementation of Impact of Lung Function on Other-cause Death in Adult/Adolescent Model

The adult/adolescent model for dupilumab included an option to consider the impact of lung function on other-cause mortality, thus allowing to use the differences observed between treatments in terms of lung function improvements to determine different mortality rates for each treatment.

In this instance, general population life tables were adjusted based on lung function levels for each treatment (see details in the Adjustment of Other-cause Mortality based on Lung Function section), expressed in terms of FEV1 as a percentage of predicted (ppFEV1), and it was assumed that the differences in ppFEV1 between treatments remain constant whilst patients are on the treatment.

A hazard ratio (HR) of other-cause mortality was estimated for each treatment, based on the distribution of patients across different levels of ppFEV1 (≥80%; 50%–79%; <50%) and the HR of other-cause mortality for each of these three different categories of ppFEV1 levels (details are provided in the Adjustment of Other-cause Mortality based on Lung Function section).

These HRs obtained for the different treatments were then normalised via the use of assumptions to determine the excess mortality of the population and treatment modelled as compared to the general population. The possible assumptions considered were:

- Other-cause mortality risk in patients treated with background therapy is equivalent to the general population: Excess mortality versus the general population for the monoclonal antibodies is estimated by dividing the calculated HR of mortality for patients treated with the monoclonal antibodies (compared with a cohort with ppFEV1>80%) by the HR of mortality for patients treated with background therapy (compared with a cohort with ppFEV1>80%). This assumption would result in a lower other-cause mortality risk compared with the general population for patients treated with monoclonal antibodies.
- Other-cause mortality risk in patients treated with the monoclonal antibody associated with the largest improvements in FEV1 is equivalent to the general population: This assumption would result in an equivalent other-cause mortality risk to the general population for patients treated with monoclonal antibody associated with the largest improvement in FEV1. Excess mortality versus the general population for other treatments is estimated by dividing the implied HR of mortality for patients treated with the comparator (compared with a cohort with ppFEV1>80%) by the HR of mortality for patients treated with the reference therapy (compared with a cohort with ppFEV1>80%).
- Include ppFEV1 data for the general population and estimate HR versus the general population: This is the most appropriate assumption; however, this option is hampered by data availability. Generally, studies evaluating lung function focus on patients with respiratory diseases; thus, limited data—if any—are anticipated to inform these inputs based on a pure general population. Subject to availability of ppFEV1 values in the general population, excess mortality versus the general population is estimated by dividing the implied HR of mortality for patients treated with the comparator (compared with a cohort with ppFEV1>80%) by the HR of mortality for the general population (compared with a cohort with ppFEV1>80%).

The normalised HRs were then applied to the other-cause mortality data obtained from life tables for each treatment separately. For monoclonal antibodies, two separate HRs were estimated for all patients and for responders only, similarly to the approach used for efficacy outcomes. Therefore, different HRs were used for the period prior to and after response assessment.

Appendix Q. Deriving Transition Probabilities for Other Monoclonal Antibodies

In the adult/adolescent model, transition probabilities between the live health states were obtained from the LIBERTY ASTHMA QUEST (patients not on OCS) and VENTURE (patients on OCS) trials for dupilumab and for background therapy alone (see section with transition probabilities). In order to derive transition probabilities for the other monoclonal antibodies, their RRs were applied to the transition rates associated with dupilumab following the process described further below.

- The transition probability to severe exacerbation was first calculated. If we consider an example where we estimate the transition probabilities for mepolizumab (all patients), the transition probability to severe exacerbation was calculated as:

$$(P_{i,SevExac})_{Mepo} = 1 - \exp\left(-RR_{SevExac_{MepoVs.Dupi}} \times \left(R_{i,SevExac}\right)_{Dupi}\right)$$

  where $(P_{i,SevExac})_{Mepo}$ is the probability of transitioning to the 'Severe Exacerbation' state from a given state i for mepolizumab patients, $(R_{i,SevExac})_{Dupi}$represents the same transition rate for dupilumab patients (estimated as $1 - \ln\left(1 - \left(P_{i,SevExac}\right)_{Dupi}\right)$, and $RR_SevExac_{MepoVs.Dupi}$is the relative rate of experiencing severe exacerbation for mepolizumab compared to dupilumab.

  If this operation resulted in a value greater than 1, then the transition probability to severe exacerbation for mepolizumab was restricted to 1.

- The probability of transitioning to moderate exacerbation from the same given state i was then calculated, in the same manner, using the RR of experiencing moderate exacerbations for mepolizumab versus dupilumab:

$$(P_{i,ModExac})_{Mepo} = 1 - \exp\left(-RR_{ModExac_{MepoVs.Dupi}} \times \left(R_{i,ModExac}\right)_{Dupi}\right)$$

- Likewise, the transition probability to moderate exacerbation for mepolizumab was restricted to $1 - (P_{i,SevExac})_{Mepo}$(this ensures that $(P_{i,ModExac})_{Mepo} + (P_{i,SevExac})_{Mepo}$cannot be greater than 1).

- In the four-sub-state model, the probability of transitioning to the 'No exacerbation' state from the same given state i was then obtained simply as:

$$(P_{i,NoExac})_{Mepo} = 1 - (P_{i,ModExac})_{Mepo} - (P_{i,SevExac})_{Mepo}$$

- In the five-sub-state model:

  - The probability of transitioning to the 'Uncontrolled asthma' state from the same given health state i was obtained in a similar manner:

$$(P_{i,Uncontr})_{Mepo} = 1 - \exp\left(-RR\_Uncontr_{MepoVs.Dupi} \times (R_{i,Uncontr})_{Dupi)}\right)$$

  Again, this transition probability to the 'Uncontrolled asthma' state was restricted so that it could not be greater than $1 - (P_{i,SevExac})_{Mepo} - (P_{i,ModExac})_{Mepo}$.

  - The probability of transitioning to the 'Controlled asthma' state from the given state i was then simply obtained as:

$$(P_{i,Contr})_{Mepo} = 1 - (P_{i,Uncontr})_{Mepo} - (P_{i,ModExac})_{Mepo} - (P_{i,SevExac})_{Mepo}$$

Appendix R. Response Rates for Other Monoclonal Antibodies by Population

Table 134. Proportion of Patients Achieving Response with Mepolizumab

Population	% Responders	n/N	Criteria	Source
ITT population	90.9%	350/385	Patients who experience an increase in annualised exacerbation rate are discontinued	NICE TA431, company evidence submission, Table 104 (based on MENSA trial)
Company proposed population excluding OCS users with < 4 exacerbations: EOS ≥ 150 cells/µl; ≥ 4 exacerbations	97.1%	99/102		
Company proposed population: EOS ≥ 150 cells/µl; ≥ 4 exacerbations in previous year or dependency on OCS	92.3%	132/143		
ITT population restricted to maintenance OCS patients	83.0%	83/100	Patients for whom exacerbation rate improves	NICE TA431, company response to ACD, Appendix 2 (based on MENSA trial)
≥ 4 exacerbations in previous year or dependency on OCS	89.5%	170/190		
EOS ≥ 300 cells/µl; ≥ 4 exacerbations in previous year or dependency on OCS	89.2%	157/176		
EOS ≥ 300 cells/µl in previous year; ≥ 4 severe exacerbations in previous year or dependency on OCS (reimbursed population)	76.7%	122/159	≥ 50% reduction in exacerbation rate versus baseline*	NICE TA431, company response to the second ACD, Table 9 (based on MENSA trial)
	84.3%	134/159	≥ 30% reduction in exacerbation rate versus baseline	

* Continuation criterion specified in FAD for mepolizumab, alongside clinically significant reduction in continuous OCS use while maintaining or improving asthma control.

Table 135. Proportion of Patients Achieving Response with Omalizumab

Population	% Responders	Confidence Interval	Trial
ITT population	56.5%	49.7%–63.2%	INNOVATE*
	69.9%		EXALT‡
	82.4%		APEX†
Patients who experienced a hospitalisation for asthma in the year prior to enrolment in the study	56.6%	46.0%–67.3%	INNOVATE*
	56.9%		EXALT‡
	82.7%		APEX†
Patients receiving maintenance OCS at randomisation	46.9%	33.0%–60.9%	INNOVATE*
	52.5%		EXALT‡
	78.9%		APEX†
≥ 3 exacerbations in previous year	46.5%	36.0%–57.1%	INNOVATE*

NICE recommendation: people aged 6 or older who need continuous or frequent treatment with OCS (defined as 4 or more courses in the previous year).

*Double-bind, ‡Open label, †Observational

Source: Norman et al. (2013), Tables 49, 65 and 96. Assessment of response based on reported GET

Appendix S. OCS-related Adverse Events – Sources Evaluated (for Adult/Adolescent Model)

Table 136. Published Studies in the UK and US Assessing Influence of OCS on Risk of Adverse Events

Reference	Country	Database	Sample	Enrolment/ Follow-up	Population	Control Variables	Outcomes	Challenge

Bloechliger 2018(115)	UK	CPRD	165,900–269,368	2000–2015	Patients aged 18 years or older with incident or prevalent asthma requiring at least GINA Step 2 treatment	• Non-OCS users
						• Ever users
						• Current users
						  • Average daily dose ≤ 1 mg
						  • Average daily dose > 1–≤ 5 mg
						  • Average daily dose > 5 mg
							Incidence and ORs for control variables for:
							• Bone-related conditions
							• Hypertension
							• Peptic ulcer
							• Severe infections
							• Herpes zoster
							• Diabetes mellitus
							• Cataract
							• Glaucoma
							• Chronic kidney disease
							• Affective disorders
							• Cardiovascular events
								• Inputs required on QoL and costs

Mepolizumab submission to NICE, 2016(64)	UK	CPRD	Not reported	2004–2012	Severe asthma patients defined by GINA guidelines Step 4/5	Additional gram of average cumulative maintenance OCS dose (over 28-day period) versus no use	Relative risk of event due to additional gram of average cumulative maintenance OCS dose (over 28-day period) versus no OCS use, for: • Diabetes • Myocardial infarction • Osteoporosis • Peptic ulcer • Cataract	• Inputs required on QoL and annual risk of events • Limited details on methods
Sweeney 2016(123)	UK	British Thoracic Society Difficult Asthma Registry	Severe asthma: 770	Not reported	GINA Step 5 treatment and ≥ 4 prescriptions for OCS in each of two consecutive study years	• CS-dependent asthma • Required daily systemic CS therapy to maintain asthma control • Non-CS dependent asthma	ORs for: • Endocrine disorder • Cardiac disease • Osteoporosis • Obesity • Sleep disorders • Eye diseases • Dyspeptic disorders • Psychiatric disorders • Skin conditions Specific conditions within each category listed	• May not capture benefit of dose reduction (only withdrawal) • Inputs required on QoL and annual risk of events

Walsh 2001(124)	UK	Questionnaire to 41 general practices close to Nottingham	451	Not reported	Men and women aged 50 years or more with a diagnosis of asthma, COPD, or fibrosing alveolitis if they required either (a) continuous OCS, defined as daily or alternate day OCS therapy for at least the last 6 months or (b) frequent intermittent courses of OCS, defined as a mean daily dose of 5 mg prednisolone (or equivalent dose of other corticosteroid) over the previous 6 months	• Patient taking OCS and evaluated by quartile (mean cumulative gram) • Corticosteroid quartile 1: 5.1 (1.1–7.7) • Corticosteroid quartile 2: 11.7 (7.8–16.3) • Corticosteroid quartile 3: 23.6 (16.4–37.4) • Corticosteroid quartile 4: 60.6 (37.6–186) • Control patients	OR for steroid-dependent (also by quartile) versus control: • All fracture • Vertebrae • Ribs sternum • Cataract • Bruising • Muscle weakness	• Not specific to an asthma population • Not all potential OCS-related AEs captured • Evidence may be outdated
Manson 2009(116)	UK	Literature search	Not applicable	Studies published between 1990–2007	Papers measuring prevalence of OCS adverse effects among oral steroid users, the relationship between the presence of OCS side effects and patient characteristics such as treatment history, age, gender, or	Not applicable	Cost per patient year of OCS-related AE	• Literature search not specific to asthma or population of interest • Evidence may be outdated

					duration of steroid use, the dose-response relation-ship			
Zazzali 2015(125)	US	Commercial health care claims	37,123	2008–2009	Patients ≥ 18 years of age who had ≥ 2 medical claims with asthma as one of the listed diagnoses and had filled ≥ 2 asthma medications	• High OCS • Patients with ≥ 30 annual days of supply (cumulative annual dose 1,260 mg) • No OCS • Patients with < 30 annual days of supply (cumulative annual dose 250 mg)	Risk of AEs in patients with no OCS versus high OCS: • Any AE • Bone-related conditions • Osteoporosis • Fractures • Pneumonia • Opportunistic infections • Hypertension • Diabetes • Glaucoma • Cataracts • Lipid disorders • Obesity • Peptic ulcer disease	• May not capture benefit of complete withdrawal • Inputs required on QoL • Not specific to patients with uncontrolled persistent asthma
Lefebvre 2017(126)	US	Medicaid claims data	SGC users: 3,628 No SGC: 26.987	1997–2013	> 12 years of age, with > 2 administrative claims associated with an asthma diagnosis (ICD-9-CM code 493.xx)	• SGC users: chronic SGC use of ≥ 6 months duration (defined as ≥ 5 mg daily prednisone dose equivalent with no gap between two SGC claims ≥ 14 days) • Low SGC exposure: ≤ 6 mg/day • Medium SGG exposure: >6–<12 mg/day • High SGC exposure: ≥ 12 mg/day • No SGC	OR for complications versus no SGC: • Gastrointestinal • Infections • Bone- and muscle-related • Cardiovascular • Haemato-logic/onco-logic • Metabolic • Ocular • Psychiatric • OR for resource use versus no SGC: • ER visit • Outpatient visit • Inpatient visit • Pharmacy dispensing • Other visit Annual incremental costs and costs associated with incidence of complications	• Inputs required on QoL and annual risk of events • Not specific to patients with uncontrolled persistent asthma
Sullivan 2017(127)	US	MarketScan	Before matching	2000–2014	Asthmatic patients aged 18 years and older with continuous	OCS prescriptions: • Current 1–3 prescriptions • Current ≥ 4 prescriptions	OR for incident new AE and for: • Osteoporosis • Fracture • Metabolic syndrome	• No regard to dose or duration of OCS • Inputs required on QoL

OCS cohort: 72,603 No OCS cohort: 156,373	enrolment for 12 months or more before and 24 months or more after the index date	• No. of prior years with 1–3 prescriptions • No. of prior years with ≥ 4 prescriptions • No. of years with 1–3 prescriptions • No. of years with ≥ 4 prescriptions	• Hypertension • Obesity • Type 2 diabetes • Dyslipidaemia • Avascular necrosis • Gastrointestinal ulcers/bleeds • Tuberculosis • Cataract • Glaucoma	and annual risk of events • Not specific to patients with uncontrolled persistent asthma

Appendix T. Asthma-related Mortality

Sources Evaluated to Inform Asthma-related Mortality in UK Adult/Adolescent Model

Table 137. Studies Assessing Mortality after a Hospitalisation or Exacerbation (UK and US)

Ref	Country	Years Of Enrolment	Population	Database	Outcome Data	Stratification	Results	Challenge
Watson 2007(67)	UK	2000–2005	Patients hospitalised under ICD-10 codes J45 ("asthma") and J46 ("acute severe asthma") between April 2000 and March 2005	Camper Healthcare Knowledge Systems (CHKS) database	Proportion of deaths in patients with asthma-related admission (for ICD-10 code J45 and for code J46)	By age band (<12, 12–16, 17–44 and ≥45 years)	Results presented per 100 acute severe asthma admissions by age group -0–11: 0.97 (0.42–1.91) -12–16: 0.319 (0.104 – 0.742) -17–44: 0.383 (0.267 – 0.529) - 45+: 2.478 (2.129 – 2.865)	Data provided for acute severe asthma admission, requiring external sources to inform mortality in non-hospitalised severe exacerbations Death may not necessarily be attributed to asthma exacerbation Population is not restricted to patients with uncontrolled persistent asthma Data provided for age group ≥45 years, requiring

								assumptions or external data to inform variation in mortality above the age of 45
CHKS updated analysis 2016**(120)**	UK	2000–2015	All patients admitted (emergency admission only) with specific asthma-related code J46 ("acute severe asthma"; status asthmatics) as primary reasons their first episode within a spell were included, within the time period April 1, 2000–March 31, 2015	CHKS database	Asthma-related mortality post admission	By age band (0–11, 12–16, 17–44, 45–54, 55–64, ≥65 years)	0–11: 0.07% 12–16: 0.18% 17–44: 0.30% 45–54: 0.92% 55–64: 1.52% 65+: 4.55%	Population is not restricted to patients with uncontrolled persistent asthma Death may not necessarily be attributed to asthma exacerbation Limited information on methodology
De Vries 2010**(69)**	UK	1993–Not reported (average follow-up 5 years)	Patients aged ≥18 years who received a prescription for inhaled SABA or LABA after 1 January 1993. Patients coded as COPD were excluded.	UK General Practice Research Database (GPRD), linked to the national registry of hospital admission (hospital episode statistics [HES])	Incidence rates of asthma death for status asthmaticus during current exposure	By treatment step (using the BTS/SIGN guidelines of 2005)	Asthma death rate between 0.01 and 0.4 per 100 person-years, depending on treatment step	Rates of death are not reported specifically for patients with exacerbations, rather by treatment step Classification of patients based on BTS/SIGN guidelines in 2005,

								which varies from 2017 guidance
Roberts 2013**(68)**	Scotland	1981–2009	All asthma hospitalisations for adults (>18 years) with ICD-9 code 493 and ICD-10 codes J45-J46 in the principal diagnostic position at discharge (1981–2009)	Scottish Morbidity Record Scheme (SMR01) linked to General Register Office for Scotland (GROS)	Odds ratio for 30-day case-fatality after asthma admission	Odds ratio by age band (18–24, 25–34, 35–44, 45–54, 55–64, ≥65 years)	Crude 30-day case-fatality rate of 0.9%. Based on odds ratios and distribution of cohort, this implies a risk between 0.20%–2.52% depending on age	Death may not necessarily be attributed to asthma exacerbation Data provided for asthma admission, requiring external sources to inform mortality in non-hospitalised severe exacerbations Population is not restricted to patients with uncontrolled persistent asthma
Sheikh 2016**(128)**	Scotland	2001–2010	Not reported	NHS Scotland hospital discharge and death records (Scottish Health and Ethnicity Linkage Study)	Risk of death	Not applicable	Death was an infrequent occurrence 0.4% of first asthma events	Data not provided by age group Death may not necessarily be attributed to asthma exacerbation Population is

								not restricted to patients with uncontrolled persistent asthma
Kaur 2015**(129)**	US	2001–2010	Patients with a primary diagnosis of asthma (ICD-9-CM code: 493)	Nationwide Inpatient Sample (NIS) database between 2001–2010	In-hospital mortality	By age 5–14, 15–34, 35–54, 55–74, 75+	In-hospital mortality by age: - 5–14: 0.08% -15–34: 0.26% -35–54: 0.49% -55–74: 1.35% -75+: 3.02%	Death may not necessarily be attributed to asthma exacerbation Data provided for asthma admission, requiring external sources to inform mortality in non-hospitalised severe exacerbations Population is not restricted to patients with uncontrolled persistent asthma
Sullivan 2009**(130)**	US	Not reported	Severe asthma patients, hospitalised for asthma	Closed panel health maintenance organisation	30-day risk of death following hospitalisation or exacerbation for asthma	Not applicable	30-day risk of death following hospitalisation for asthma was 2.48% (0.5%–7.1%)	Only available in abstract form with limited details on methodology Age distribution

							and following an exacerbation was 1.1% (0.2%–3.1%)	of patients or risks by age are not provided
Krishnan 2006(131)	US	2000	Hospital admissions with a primary discharge diagnosis of asthma or respiratory failure with secondary diagnosis of asthma	Nationwide Inpatient Sample (NIS) 2000 data	In-hospital mortality	By age 5–14, 15–34, 35–54, 55–74, 75+	Overall hospital mortality for asthma exacerbations was 0.5% (0.4%–0.6%). By age: - 5–14: 0.02% -15–34: 0.2% -35–54: 0.3% -55–74: 0.8% -75+: 1.9%	Data may be outdated and appears to be at the lower spectrum as compared to other published literature Death may not necessarily be attributed to asthma exacerbation Data provided for asthma admission, requiring external sources to inform mortality in non-hospitalised severe exacerbations Population is not restricted to patients with uncontrolled

Asthma-related Mortality in Previous Models

Economic evaluations identified as part of the SLR for the adult/adolescent model were further reviewed to determine inputs used to inform the fatality rates associated with exacerbations. Previous models generally assumed that the rate of death due to exacerbations was independent of age, with values ranging between 0.043%–3.11%. Lower estimates of 0.1%(61) and 0.043%(87) reported in these models are unlikely to be applicable as they are based on rates of asthma death in patients treated with OCS rather than probability of death after an exacerbation(69) and a converted per-cycle risk (rather than per event).(87)

Table 138. Input Values Used to Model Death due to Exacerbation in Previous Models

Study	Fatality rate associated with exacerbation	Applied to	Source
Institute for Clinical and Economic Review, 2015**(63)**	2.48%	Severe exacerbations leading to hospitalisation	Watson et al., 2007(67)
Institute for Clinical and Economic Review, 2018**(132)**	1.79%	Exacerbation-related ED visits	NRAD 2014(70)
	2.48%	Exacerbation-related hospitalisation	Watson et al., 2007(67)
Norman et al., 2013**(61)**	0.1%	Severe exacerbations	de Vries et al., 2010(69)
Brown et al., 2007**(133)**	3.11%	Severe exacerbations	Lowhagen et al., 1997(134)
Campbell et al., 2010**(85)**	1.10%	Severe exacerbations leading to hospitalisation	Sullivan et al., 2009(130)
Dewilde et al., 2006**(135)**	2.08%	Severe exacerbations	Lowhagen et al., 1997(134) and assumptions based on INNOVATE trial
Lam et al, 2018**(136)**	1%	In-hospital mortality rate from an exacerbation	Kaur et al, 2015(137)
Morishima et al., 2013**(138)**	1.55%	Unclear	Japanese Vital statistics
Nguyen et al., 2017**(87)**	0.043%	Severe exacerbations	Sullivan et al., 2009(130)
Sullivan et al, 2020**(139)**	1.8%	Exacerbation requiring emergency room visit	NRAD 2014(70)
	2.5%	Exacerbation requiring hospitalisation	de Vries et al., 2010(69)
Suzuki et al., 2017**(140)**	2%	Severe exacerbations	Brazilian statistics
van Nooten et al., 2013**(141)**	2.48%	Severe exacerbations	Watson et al., 2007(67)
Whittington et al., 2017**(88)**	2.48%	Severe exacerbations leading to hospitalisation	Watson et al., 2007(67)

Three previous HTA models for asthma biologics used varying probabilities of death due to asthma exacerbations dependent on age (60, 64, 65), with two specifically reporting the values used (Table 139)(64, 65, 81). The other assessment did not report the values used but reported use of odds ratios from a study by Roberts and colleagues(68) which were applied to UK life tables (60).

Table 139. Input Values Used to Model Death due to Exacerbation in the Mepolizumab Submission to NICE (64, 81)

Age group	p (%) applied to the rate of exacerbations requiring a hospitalisation	p (%) applied to the rate of exacerbations requiring ED visit	p (%) applied to the rate of exacerbations requiring OCS

Manufacturer submitted base case			
<12	0.10%	0.07%	0.01%
12–16	0.32%	0.23%	0.05%
17–44	0.38%	0.28%	0.06%
≥45	2.48%	1.79%	0.38%
Revised base case / accepted			
12–16	0.176%	0.23%	0.05%
17–44	0.295%	0.28%	0.06%
45–54	0.923%	1.79%	0.38%
55–64	1.523%	1.79%	0.38%
≥65	4.545%	1.79%	0.38%

Discussions in NICE assessments of previous biologics on the appropriate source to use are summarised in Table 140 below.

Table 140. Decision-making Process for Source of Asthma-related Mortality in Previous Submissions of Monoclonal Antibodies to NICE

Submission	Approaches used for estimation of asthma-related mortality
Mepolizumab (TA431)(64, 81)	Manufacturer's submission: Conducted systematic review and found two studies relevant and informative for UK: Watson et al. 2007(67) and Roberts et al. 2013 (68). Watson was deemed preferable to Roberts, "since Roberts required absolute deaths to be estimated that may differ from the observed data, the definition of severe asthma was not specifically defined and the long study period over which care is likely to have changed." Base case: **Watson et al. 2007 + NRAD** • Watson et al. provide mortality data for asthma-related hospitalisation. Those were used for clinically significant exacerbations leading to hospitalisations in the model of mepolizumab, for the age bands provided by Watson et al. • To derive mortality data for other types of clinically significant exacerbations in the model (i.e., requiring use of systemic CS or requiring an ED visit), the NRAD was used as a source of data on asthma death by location (in community / on the way to hospital / in hospital). The manufacturer assumed that all the mortality data in NRAD applied to their population of interest (i.e., regardless of asthma severity, eosinophilic status, etc) and assumed that the proportion of asthma deaths occurring in the community could be applied for exacerbations requiring systemic CS and the proportion of asthma deaths occurring on the way to the hospital could be applied for exacerbations requiring an ED visit. Scenarios: • Watson 2007 alone (therefore, asthma-related death is only considered for exacerbations requiring hospitalisation) • Midpoint between estimates from Watson 2007 and from de Vries 2010 (69), plus 15% to represent a very severe uncontrolled asthma population (approach taken in omalizumab submission TA278) • Midpoint between estimates from Watson 2007 and from de Vries 2010 • Roberts 2013 Main ERG/Assessment Group/NICE critiques and/or recommendations: • Watson et al. used age categories but used a constant rate for those aged ≥ 45 years. The ERG deemed inappropriate to use a constant mortality rate for patients aged ≥ 45 years, as evidenced by the data reported by Roberts et al. The ERG recommended to use the stratification as in Roberts et al. (45–54, 55–64 and ≥ 65 years), which account for the increase in mortality rates after the age of 45 years whereas those from Watson et al. do not.

	• Should any of the deaths in Watson et al. be assignable to the 'hospital, pre-hospital arrest' category (in NRAD), then the number of deaths due to asthma exacerbations would be overestimated. Manufacturer's additional analyses in response to critiques/comments: The company undertook a retrospective cohort analysis using the same database as that used to inform Watson et al. (the CHKS database) and performed two exploratory analyses using Watson et al. + Roberts et al. with two different approaches: • Applying the rate ratios derived from comparing the rate for the 35-44 age band with the other age bands as reported by Roberts et al. to the mortality rate reported by Watson et al. for the 17-44 age band (option 1) • Assuming the same number of exacerbations across the three age bands and fitting the total deaths reported by Watson et al. in a way that the relative RRs of the different age bands were similar to those reported by Roberts et al. (option 2). ➔ The ERG preferred option 2.
Reslizumab (TA479)(60, 142)	Manufacturer's submission: Used **Roberts et al. 2013.** Also considered Watson et al. 2007 but chose Roberts chosen "as it stratifies patients into narrower age bands than those in Watson et al.". Applied the odds ratios from Roberts et al. to the national UK life tables. Main ERG/Assessment Group/NICE critiques and/or recommendations: This was not criticised by the ERG nor by the NICE committee.
Omalizumab (TA278)(61, 143)	Manufacturer's submission: Conducted a systematic review and identified 5 studies conducted in the UK: • Watson et al. 2007(67) • Gupta et al. 2004(144) and Wildman et al. 2009(145) but reported mortality following admission to the ICU. • Kearney et al. 1998,(146) Seddon and Heaf 1990,(147) and Gupta et al. 2004 but reported mortality in patients who required mechanical ventilation. Base case: **Watson et al. 2007** as manufacturer concluded that it "provided the only UK-specific data on the mortality risk from exacerbations resulting in non-ICU related hospitalisations". Scenarios: • Watson et al. 2007, but applying the mortality estimate not stratified by age • Lowhagen et al. 1997(134) (this was the source used in the original submission [TA201], a Swedish observational study on data collected between 1988 and 1990) • Gupta et al. 2004 (see above) Main ERG/Assessment Group/NICE critiques and/or recommendations: • Watson et al. provide mortality risk following hospitalisation for acute severe asthma, while in the model it is applied to all clinically significant severe (CSS) exacerbations: this may have resulted in an overestimation of asthma deaths because only about 20% of CSS exacerbations in the clinical trial from which the exacerbation data originated (INNOVATE) involved hospital admissions. • Manufacturer did not apply the age-dependent rates from Watson et al. but instead used the value for ≥ 45 years for the whole population (mean starting age of cohort was 43 years old). Assessment Group's model: The Assessment Group also conducted a systematic review and identified two potential sources: de Vries et al. 2010 and Watson et al. 2007. Elected to use de Vries et al. since the GPRD study reported data stratified by severity and included deaths in the community. Base case: **de Vries et al. 2010** (used the value estimated for Step 5 in BTS/SIGN guidelines) • Mortality risk applied to all patients in the model.

- Not stratified by age.

Scenarios:

- For patients < 18 years of age only: Watson et al. 2007 (using ICD10 code J46, i.e., for acute severe asthma)
- For all patients: Watson et al. 2007 (ibid)

Comparing the two sources, the Assessment Group identified that the risk of mortality was similar for patients aged 12-44 years but for patients ≥ 45 years, the risk of asthma-related death reported in de Vries was about one fifth of the risk reported by Watson. However, this was considered consistent with Watson since approximately 20% of the clinical significant severe exacerbations in INNOVATE involved hospitalisation.

Additional analyses requested from Assessment Group by the Appraisal Committee at the 1st Appraisal Committee meeting:

New analyses conducted for three particularly severe subpopulations.

Base case: **Watson et al. 2007**

Scenarios:

- **Watson et al. 2007 + 15% (to represent the most severe asthma population)**
- **de Vries et al. 2010 + 15% (ibid)**

Additional analyses submitted by the manufacturer after the 2nd Appraisal Committee meeting:

Midway between the estimates from Watson et al. and de Vries et al. + 15%.

This approach was the one used for the determination of what was the eventual "most plausible ICER" in the omalizumab appraisal.

The Appraisal Committee concluded that the 15% increase in mortality risk was an appropriate approximation of the mortality risk in very severe allergic asthma.

The Appraisal Committee also concluded that a more realistic mortality rate likely lays between the midpoint and the estimate from de Vries et al.

The Appraisal Committee concluded that both the Watson et al. and the de Vries et al. studies had limitations, that considerable uncertainty remained about the mortality associated with severe persistent asthma, and that neither may reflect mortality among the subgroups of people with very severe persistent asthma.

Appendix U. Treatment-dependent Utility Values Used in Earlier Evaluations

Previous HTA submissions and economic evaluations have considered the following as predictors of HRQoL:

- Treatment(61, 63, 64, 85, 133, 141, 148, 149)
- Response to treatment(61, 64, 85, 88, 133, 141, 148)
- Degree of asthma control(60, 150)
- Asthma exacerbations(60, 61, 63, 64, 85-87, 133, 138, 141, 148-154)
- Asthma symptoms(138)
- Lung function(89)
- OCS-related AEs(61, 63, 64)

Table A1. Utility Values by Treatment used in Previous Economic Evaluations

Study	Population	Methodology	Source	Add-on Treatment	Utility value			Incremental Utility Add-on versus SoC	
					SoC	Add-on Treatment: All patients	Add-on Treatment: Responders	All patients	Responders
NICE, 2016, TA431(64)	Adults with severe eosinophilic asthma: ITT population	SGRQ mapped to EQ-5D	MENSA trial	Mepolizumab	0.738	0.796	0.806	0.058	0.068
		EQ-5D	DREAM Phase IIb		0.794	0.802	0.824	0.008	0.03
	GSK proposed population excluding mOCS users with < 4 exacerbations	SGRQ mapped to EQ-5D	MENSA trial		0.682	0.793	0.805	0.111	0.123
		EQ-5D	DREAM Phase IIb		0.797	0.829	0.834	0.032	0.037
	GSK proposed population: blood eosinophil count of 150 cells/µl at initiation of treatment and 4 or more exacerbations in the previous year or were dependent on systemic corticosteroids	SGRQ mapped to EQ-5D	MENSA trial		0.708	0.777	0.795	0.069	0.087
		EQ-5D	DREAM Phase IIb		0.785	0.827	0.837	0.042	0.052
Institute for Clinical and Economic Review, 2015(63)	Adults with severe, uncontrolled asthma and evidence of eosinophilic inflammation, treated with high-dose ICS therapy and at least one additional controller medication	SGRQ mapped to EQ-5D	MENSA trial	Mepolizumab	0.77	0.828		0.058	
Whittington et al., 2017(88)	Adults with severe uncontrolled asthma and evidence of eosinophilic inflammation	SGRQ mapped to EQ-5D	MENSA trial	Mepolizumab	0.77	0.828		0.058	
Norman et al., 2013(61)	Patients uncontrolled at Step 4, and in the process of moving up to Step 5 (maintenance OCS), and patients controlled at Step 5	EQ-5D	EXALT trial	Omalizumab	0.719		0.767		0.048

	whose asthma would be uncontrolled if they were on Step 4 therapy								
	As above, restricted to patients experiencing a hospitalisation in the year prior to enrolment				0.631		0.761		0.13
	Restricted to patients receiving maintenance OCS at randomisation				0.686		0.791		0.105
Brown et al., 2007(133)	Patients with severe persistent allergic asthma despite high-dose ICS plus LABA	Mini-AQLQ mapped to EQ-5D	ETOPA trial	Omalizumab	0.65		0.82		0.17
Campbell et al., 2010(85)	Adults with moderate-to-severe persistent asthma, a positive skin test or in vitro reactivity to a perennial aeroallergen, and symptoms inadequately controlled with ICS	AQLQ mapped to EQ-5D	INNOVATE	Omalizumab	0.669	0.732	0.779	0.063	0.11
Dewilde et al., 2006(148)	Adult patients suffering from severe persistent, IgE-mediated allergic asthma who are uncontrolled despite GINA Step 4 therapy	AQLQ mapped to EQ-5D	INNOVATE	Omalizumab	0.669		0.779		0.11
Suzuki et al., 2017(140)	Patients with uncontrolled severe allergic asthma in a Brazilian healthcare setting	AQLQ mapped to EQ-5D	eXpeRience Study	Omalizumab	0.608	0.81	0.821	0.202	0.213
van Nooten et al., 2013(141)	Adult patients (≥12 years) with uncontrolled allergic (IgE mediated) asthma despite treatment with high-dose ICS (>1000 mg beclomethasone) and a LABA	Reported to be EQ-5D; however assumptions are unclear	PERSIST Study	Omalizumab	0.611		0.763		0.152

Appendix V. Summary of study results dupilumab, children with type 2 inflammation

Outcome	Dupilumab (n=236)	Placebo (n=114)	AD (95% CI)	RD (95% CI)	p-value
Efficacy results					
Annualized rate of severe asthma exacerbations during 52-week treatment period (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with at least 1 severe asthma exacerbation event during the 52 week period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from BL at week 12 of ppFEV1, (±SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% patients with >=200mL improvement in FEV1 at week 12 (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from BL at week 24 of ACQ-7-IA, (±SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from BL at week 52 of PAQLQ-IA global score (+SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from BL at week 52 of PRQLQ global score (+SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD, Absolute difference; RD, Relative difference; BL, baseline; CI, Confidence Interval; NA, not available; ppFEV1, predicted prebronchodilator FEV1; RD. **Note:** #, p-value for AD; *, p-value for RD. Type 2 inflammation is defined as peripheral eosinophils (≥0.15 Giga/L) and/or elevated FeNO (≥20 ppb)

Appendix X. Efficacy and safety of dupilumab dosing Q4W

The q4w dosing is approved by the European Medicines Agency and the scientific background is described in the EPAR. The dosing of dupilumab in Denmark in children 6 to 11 years of age with asthma is illustrated in Table1. Evidence supporting the dosing is included.

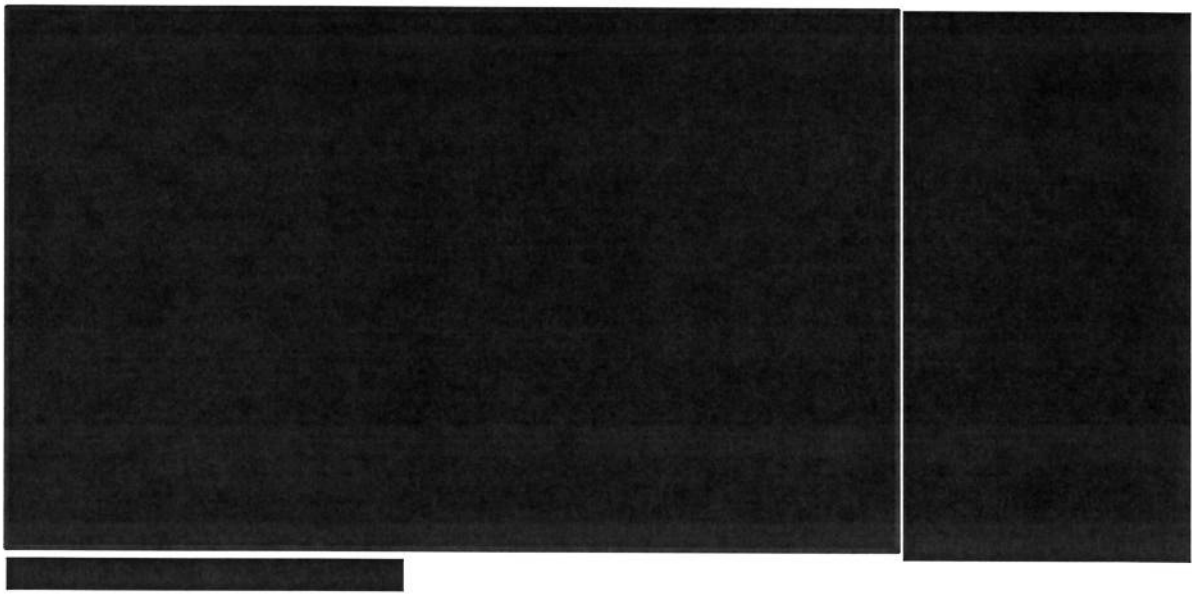
Table 1. Dose of dupilumab for subcutaneous administration in children 6 to 11 years of age with asthma

Body weight	Initial and subsequent dosing	Evidence supporting the dosing
15 to less than 30 kg	300 mg every four weeks (Q4W)	Pharmacokinetic analyses showing comparable simulated and observed steady-state dupilumab trough concentrations following dupilumab 300 mg q4w (simulated) and dupilumab 100 mg/200 mg q2w (actual) in pediatric patients (comparable dose-exposure) Additional supportive data is provided by the descriptive efficacy and safety of patients exposed to 300 mg q4w in the VOYAGE extension study (EXCURSION)
30 kg to less than 60 kg	300 mg every four weeks (Q4W)	Pharmacokinetic analyses showing comparable simulated and observed steady-state dupilumab trough concentrations following dupilumab 300 mg q4w (simulated) and dupilumab 100 mg/200 mg q2w (actual) in pediatric patients (comparable dose-exposure)
60 kg or more	200 mg every other week (Q2W)	Dosing investigated in QUEST (adults and adolescents)

Pharmakokinetic/exposure-response analyses

The VOYAGE study demonstrated efficacy and an acceptable safety profile of dupilumab 100 mg q2w and 200 mg q2w. Pharmacokinetic/exposure-response analyses based on data from VOYAGE demonstrate that simulation of a 300 mg q4w subcutaneous dose in children aged 6–11 years with body weight of ≥15–<30 kg and ≥30-<60 kg resulted in predicted steady-state through concentrations similar to the observed through concentrations of 200 mg q2w (≥30 kg) and 100 mg q2w (<30 kg) in children aged 6-11 years, respectively [redacted]

[redacted]



EXCURSION

Patients who completed the treatment period of the VOYAGE study could participate in the open label extension study (EXCURSION). As of the cut-off date of 25 June 2021, a total of 18 patients (8 in the placebo-dupilumab category and 10 in the dupilumab-dupilumab category) had been exposed to dupilumab 300 mg q4w for a cumulative exposure of 10.5 patient-years (mean [SD] duration of exposure: 213.9 [104.5] days). The safety profile was similar to that seen in VOYAGE.

There were no severe asthma exacerbations among the 18 patients that were exposed to 300 mg q4w dose regimen. Overall, the percentage predicted FEV1 remained stable for these individual patients over the timepoints evaluated after the switch to the dupilumab 300 mg q4w regimen in EXCURSION.

In an earlier datacut with 14 patients who were exposed to 300 mg q4w, 4 patients experienced TEAEs during their exposure to 300 mg q4w:1 in the placebo-dupilumab category (skin laceration) and 3 in the dupilumab-dupilumab category (headache and abdominal pain, injection site reaction, and scratch [right leg]). Of these 4 patients, 1 patient had a similar TEAE (injection site reaction) before switching to 300 mg q4w. None of the TEAEs reported during the 300 mg q4w exposure were serious or led to permanent treatment discontinuation.

No patients experienced SAE of asthma exacerbation and there was no treatment-emergent SAE in the patients exposed to the 300 mg q4w regimen. In addition, there were no TEAEs leading to treatment discontinuation reported in patients exposed to the 300 mg q4w regimen. Finally, no new ADRs were identified in the study.

During EXCURSION, changes in blood eosinophil mean or median from baseline were the same as the dupilumab group in the parent VOYAGE study. As to clinical chemistry, dupilumab treatment did not result in changes in electrolytes or metabolic parameters in either of the studies. Moreover, Dupilumab treatment did not result in changes in liver or renal function tests over the course of both studies (2).

QUEST

The dosing for the population ≥ 60 kg is supported by the QUEST study in adults/adolescents. When comparing data from QUEST and VOYAGE dupilumab reduced exacerbations in both the adult/adolescent and pediatric (aged 6 to < 12 years) populations with the type 2 inflammatory asthma phenotype. The magnitude of effect was similar across both populations. In the adult/adolescent study, the exacerbation reduction was 54.2% and 57.7% in the 200 mg q2w and 300 mg q2w groups, respectively and this was 59.3% for the pediatric population. Similar patterns were observed across populations selected by individual markers of type 2 inflammation including baseline eosinophils alone (eosinophils

≥ 0.15 Giga/L or eosinophils ≥ 0.3 Giga/L) or by baseline FeNO alone (≥20 ppb in children and ≥25 ppb in adolescents and adults).
Dupilumab improved lung function in both the adult/adolescent and pediatric (aged 6 to 12 years) populations with the type 2 inflammatory asthma phenotype across both studies. Despite the higher baseline mean percent predicted pre-BD FEV1 in the pediatric population, the magnitude of improvement was consistent across both populations. In the adult/adolescent study, the LS mean difference from placebo at Week 12 in percent predicted pre-BD FEV1 was 5.41% and 4.84% for the 200 mg q2w and 300 mg q2w groups, respectively and this was 5.21% for the pediatric population. Similar patterns were observed for patients identified by baseline eosinophils alone (eosinophils ≥0.15 Giga/L or eosinophils ≥0.3 Giga/L) or by baseline FeNO alone (≥20 ppb in children and ≥25 ppb in adolescents and adults) (2).

Conclusion

A weight-based dosing for pediatric patients with asthma age 6 to < 12 years was suggested as already existent for other indications. Efficacy results related to the diverse dose regimes of the Phase 3 studies were consistent for all efficacy populations. Efficacy and safety results do not give rise to any objections against this dose regimen which is already authorized for AD patients with a body weight of 15 ≤ 60 kg following a split loading dose of 300 mg each on Day 1 and 15. The analysis on efficacy results across the adult/adolescent and pediatric populations delivered similar results.
The 300 mg q4w dose is supported by PK and PK/PD analyses and simulations in children 6 to <12 years of age and in adults and adolescents with asthma, the efficacy and safety data observed in Studies VOYAGE and EXCURSION including descriptive efficacy and safety data of 300 mg q4w in Study EXCURSION, as well as supportive safety and PK data from children 6 to <12 years of age with AD from the Phase 3 study R688-AD-1652.
Overall, the dupilumab 300 mg q4w dose is anticipated to provide a benefit-risk profile similar to the 100 mg/200 mg q2w doses across weight groups.

References

(1) Data on file
(2) Dupixent, European Public Assessment Report, April 2022, Accessed via https://www.ema.europa.eu/en/documents/variation-report/dupixent-h-c-004390-x-0045-g-epar-assessment-report_en.pdf