Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende tezepelumab (Tezspire) til behandling af svær astma

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. tezepelumab
2. Forhandlingsnotat fra Amgros vedr. tezepelumab
3. Ansøgers endelige ansøgning vedr. tezepelumab

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23. marts 2023

AstraZeneca's comments for the assessment report: "*Medicinrådets(DMC) anbefaling vedr. tezepelumab til behandling af svær astma".*

Overall, the assessment report and requests for subpopulation data during the application process has been steered towards comparing tezepelumab to the previous assessment of other biologics within severe asthma. AstraZeneca understands why this is helpful for the DMC in terms of placing tezepelumab in the existing "*Behandlingsvejledning*" and tender. However, it is important to also remember that the indication for tezepelumab is broader than the other biologics, as it is the only biologic which based on its indication can be used for patients with severe asthma regardless of expression of one, or multiple elevated biomarkers or even no elevated biomarkers at defined cut offs. Tezepelumab showed improved asthma outcomes in trials irrespective of biomarkers and levels, however when a heterogenous patient population as severe asthma is, is divided into smaller more homogenous patient populations (by request from the DMC), statistically significance gets harder to show due to the size of the populations.

The T2 low population with EOS<150 and FeNO<25
It is stated in the assessment report that the effect observed in the T2 high population was not observed in the T2 low population. AstraZeneca does not agree with this statement, as it is based on a broad CI interval in the rate ratio in exacerbation rate of tezepelumab versus placebo. In the opinion of AstraZeneca, a more correct statement is that the broad CI interval is an uncertainty parameter, but not the same as no effect.
In the NAVIGATOR trial this patient population is 16% of the total patient population and when excluding patients with perineal allergy, it is only 6%. [redacted]
AstraZeneca is therefore surprised by the estimate from the DMC regarding the size of this patient population being 30% in Denmark. However, it does underline the level of unmet need in severe asthma, regardless of the introduction of multiple biologic treatments which have improved the outcome for many patients. We also support the statement from the DMC that these patients are not well treated at the current standard of care and have higher healthcare resource utilization.
AstraZeneca understands that smaller patient populations can be linked to more uncertainties in analyses. Since the Danish Severe Asthma Registry follows all severe asthma patients on biologics in Denmark, these patients will also be followed, and the effect will be documented in the registry. This registry can also follow up on the actual number of T2 low patients in Denmark, and whether this deviates from other countries/the references used.

Different ICERs
AstraZeneca acknowledges that the ICER of the DMC main analysis/base case is very similar to AstraZeneca's results. In the sensitivity analyses mortality and exacerbation multipliers are removed. To our knowledge, there is no possibility to track asthma-related mortality (ICD-10 codes J45 and J46) in the publicly available Danish statistical databases. In other Nordic countries, this possibility exists. Between 2016 and 2021, in Sweden, there were 96 to 153 asthma-related deaths, in Norway there were 80 to 110 asthma-related deaths, and in

[redacted]

[redacted]

Finland, there were between 61 to 90 asthma-related deaths. A recent study from France has shown that over two years, there was a relative risk of death of 2.35 (95% CI 1.70 to 3.29) for severe uncontrolled asthma patients (Roche et al., 2022[2]). Thus, to completely remove the mortality from the cost-effectiveness model does not represent the real-world setting. Furthermore, the argument raised by the DMC on page 7 in the *"vurderingsrapport",* which explains why the placebo group gets a good treatment response supports the use of the exacerbation multiplier in the cost-effectiveness model. An improvement in asthma control during the study period among the patients on placebo has been shown in several clinical trials compared to the pre-study period for patients with severe uncontrolled asthma. In the cost-effectiveness model of Tezepelumab, an exacerbation multiplier of 1.52 was used, which is within the rangle of the placebo effect from the other clinical studies of biologic treatments for severe uncontrolled asthma patients (Table 1).

Table 1. Exacerbation multipliers in clinical studies of biologic treatments for patients with severe uncontrolled asthma.

Clinical study	Annual exacerbations for the placebo population prior to the study period	AAER for the placebo population during the study period	Exacerbation multiplier
PATHWAY (Corren et al., 2017[3])	2.40	0.72	1.68
QUEST (Castro et al., 2018[4])	2.09	0.87	1.22
MENSA (Ortega et al., 2014[5])	3.60	1.74	1.86
SIROCCO (Bleecker et al., 2016[6])	3.00	1.30	1.70

Allergy:

AstraZeneca do agree that it is up to the treating physician to evaluate the main drivers of asthma in patients, and that allergy is not the main driver of asthma in all patients with allergy. The reason why allergy as a parameter is only included indirectly in the analysis requested by the DMC is difficult to understand as the argument is that even though a high proportion of the patient population in the trial data have allergy confirmed by sensibilization, the DMC does not think that this proves the impact of allergy in the severity of the asthma. This deviates from Swedish epidemiological evidence stating that 26-42% of total asthma incidence among younger adults can be attributed to allergic sensitization and in just over 70% of those sensitized, the asthma disease can theoretically be attributed to the sensitization itself. [7][8] AstraZeneca therefore chooses to highlight the importance of taking allergy as a parameter into account for severe asthma patients, also for the patients without co-expression of elevated EOS or FeNO.

We hope that DMC will take our comments into account before taking the final decision at the meeting on April 26th.

Kind regards
Bianca Kennedy Hall, Market Access Manager and Josefine Persson, Health Economist
AstraZeneca A/S
Nordic MC

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[2] Roche et al. Real-life impact of uncontrolled severe asthma on mortality and healthcare use in adolescents and adults: findings from the retrospective, observational RESONANCE study in France. BMJ Open. 2022;12:e060160.
[3] Corren et al. Tezepelumab in adults with uncontrolled asthma. NEJM. 2017;377:10.
[4] Castro et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. NEJM. 2018;378;26.
[5] Ortega, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. NEJM.2014;371;13.
[6] Bleecker et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2-agonists (SIROCCO): a randomized, multicentre, placebo-controlled phase 3 trial.
[7] Article in Ugeskrift for Læger by Peter Plaschke et al:https://ugeskriftet.dk/videnskab/allergi-mod-luftbarne-allergener
[8] Janson et al The European Community Respiratory Health Survey: what are the main results so far? European Community Respiratory Health Survey II. Eur Respir J 2001;18:598-611

[redacted]

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21.03.2023

DBS, BMK

Forhandlingsnotat

Dato for behandling i Medicinrådet	26.04.2023
Leverandør	AstraZeneca
Lægemiddel	Tezspire (tezepelumab)
Ansøgt indikation	Som tillægsvedligeholdelsesbehandling til voksne og unge på 12 år og derover med svær astma, der ikke er kontrolleret tilstrækkeligt på trods af høj dosis inhalationskortikosteroider plus et andet astmalægemiddel til vedligeholdelsesbehandling.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har følgende aftalepris på Tezspire (tezepelumab):

Tabel 1: Aftalepris

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	SAIP (DKK) pr. 3.4.23	Rabatprocent ift. AIP
Tezspire	210 mg	1 stk	8.677,70	[redacted]	[redacted]

Aftaleforhold

[redacted]

[redacted]

Konkurrencesituationen

[redacted]

Tabel 12: Sammenligning af lægemiddeludgifter

Lægemiddel	Sammenlignende mængde over 2 år.	Lægemiddeludgift* For 2 år. (SAIP, DKK) Priser pr.01.06.2023
Tezspire	26 doser af 210 mg	[redacted]
Nucala (mepolizumab)	26 doser af 100 mg	[redacted]
Fasenra (benralizumab)	14 doser a 30 mg	[redacted]
Dupixent (dupilumab)	53 doser a 200 mg	[redacted]
Dupixent (dupilumab)	53 doser a 300 mg	[redacted]

* lægemiddeludgiften er priserne pr.1.6.2023 som er brugt i den kommende rekommandation for svær astma.

Status fra andre lande

Land	Status	Link
Norge	N/A	
Sverige	N/A	
England	Under evaluering	

Konklusion

[redacted]

Application for the assessment of Tezspire (tezepelumab) as an add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma who are inadequately controlled with high dose inhaled corticosteroids plus another medicinal product for maintenance treatment

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1. Basic information

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Overview of the pharmaceutical	
Proprietary name	Tezspire
Generic name	Tezepelumab
Marketing authorization holder in Denmark	AstraZeneca AB SE-151 85 Södertälje Sverige
ATC code	R03DX11
Pharmacotherapeutic group	Monoclonal antibody (IgG2λ)
Active substance(s)	Tezepelumab
Pharmaceutical form(s)	Injectable solution
Mechanism of action	Tezepelumab blocks TSLP in the airway epithelium at the top of the inflammatory cascade, preventing TSLP from binding to its receptor complex
Dosage regimen	210 mg SC Q4W. No loading dose required
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Tezspire is indicated as an add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma who are inadequately controlled despite high dose inhaled corticosteroids plus another medicinal product for maintenance treatment.
Other approved therapeutic indications	No
Will dispensing be restricted to hospitals?	Yes (BEGR)
Combination therapy and/or co-medication	No, but often/always these patients also have a background medication
Packaging – types, sizes/number of units, and concentrations	Prefilled syringe and soon also as prefilled pen. 210 mg
Orphan drug designation	No

2. Abbreviations

Acronym	Definition
AAER	annualised asthma exacerbation rate

Acronym	Definition
ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
ADA	anti-drug antibodies
AQLQ	Asthma Quality of Life Questionnaire
AQLQ(S)+12	Standardised Asthma Quality of Life Questionnaire for 12 years and older
ASD	Asthma Symptom Diary
ATC	Anatomical Therapeutic Chemical
ATS	American Thoracic Society
BD	bronchodilator
BIM	budget impact model
BMI	body mass index
CEM	cost-effectiveness model
CfB	change from baseline
CGI-C	Clinician Global Impression of Change
CHMP	(European Medicines Agency) Committee for Medicinal Products for Human Use
CI	confidence interval
CRI	credible interval
CPRD	Clinical Practice Research Datalink
CSR	clinical study report
DB	Disease Burden
DKK	Danish Krone
DLS	Dansk Lungemedicinsk Selskab (The Danish Respiratory Society)
DMC	Danish Medicines Council/Medicinrådet
DSA	deterministic sensitivity analysis
DSAR	Dansk Svær Astma Register
EMA	European Medicines Agency
EOS	eosinophil
ERS	European Respiratory Society
EV	Economic Value
FAS	full analysis set
FEIA	fluorescent enzyme immunoassay
FeNO	fractional exhaled nitric oxide

Acronym	Definition
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
GINA	Global Initiative for Asthma
HR	hazard ratio
HCP	healthcare professional
HCRU	healthcare resource use
HRQoL	health-related quality of life
HTA	health technology assessment
ICD	International Classification of Diseases
ICER	incremental cost-effectiveness ratio
ICS	inhaled corticosteroid
ICU	intensive care unit
IgE	immunoglobulin E
ISAR	International Severe Asthma Registry
ITC	indirect treatment comparison
ITT	intention-to-treat
KEE	key external expert
LABA	long-acting beta-agonist
LAMA	long-acting muscarinic antagonist
LS	least squares
LTE	long-term extension
LTRA	leukotriene receptor antagonist
mSCS	maintenance systemic corticosteroids
NCT	National Clinical Trial
NMA	network meta-analysis
NNT	number needed to treat
OCS	oral corticosteroid
OR	odds ratio
PBO	placebo
PI	Product Information
PRO	patient-reported outcome
PSA	probabilistic sensitivity analysis

Acronym	Definition
QALY	quality-adjusted life year
QoL	Quality of Life
RCT	randomised controlled trial
RR	risk ratio
RWE	real-world evidence
SABA	short-acting beta-agonist
SAS	safety analysis set
SCS	systemic corticosteroid
SD	standard deviation
SGRQ	St George's Respiratory Questionnaire
SLR	systematic literature review
SoC	standard of care
STC	simulated treatment comparisons
SUA	severe, uncontrolled asthma
TLR	targeted literature review
TSLP	thymic stromal lymphopoietin
T2	type 2
VAS	visual analogue scale
WHO	World Health Organisation
WPAI	Work Productivity and Activity Impairment

3. Tables and Figures

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4. Summary

Tezepelumab will be the first biologic to receive marketing authorization regardless of biomarker profile and across phenotypes, which includes Type 2 high (including allergic asthma) and Type 2 low asthma. The GINA guideline recommends tezepelumab for patients with Type 2 high asthma, allergic asthma, as well as patients with Type 2 low asthma.

Tezepelumab has demonstrated efficacy across phenotypes and irrespective of biomarkers, as evidenced by direct clinical evidence, as well as comparable effectiveness with other biologics observed in the ITCs. Even though other biologic treatments exist, some patients with severe asthma still remain untreated or uncontrolled and switch between products, which underlines the need for a new mode of action.

This consolidates its positioning as the preferred first-line biologic across all patients with severe, uncontrolled asthma.

4.1 Tezepelumab clinical value

Tezepelumab represents a new class of biologic (anti-thymic stromal lymphopoietin [TSLP]) in the treatment of severe, uncontrolled asthma, blocking TSLP in the airway epithelium at the top of the inflammatory cascade (1-6) and interfering with multiple downstream inflammatory pathways to deliver efficacy across phenotypes and irrespective of biomarkers, including allergic, non-allergic, EOS-high and -low, and FeNO high and low populations – and even for patients with expression of multiple biomarkers. (1, 7) Beyond reducing airway inflammation, tezepelumab has been shown to have an impact on airway hyperresponsiveness, indicating that TSLP blockade might have additional benefits beyond reducing eosinophilic and allergic inflammation in asthma.

The efficacy of tezepelumab 210 mg Q4W + standard of care (SoC) in reducing the rate of asthma exacerbations and improving pulmonary function, asthma control and quality of life (QoL) in patients with severe, uncontrolled asthma was assessed in the PATHWAY (Phase IIb) and NAVIGATOR (Phase III) clinical trials. The SOURCE (Phase III) trial additionally assessed the effect of tezepelumab 210 mg Q4W + SoC versus placebo (PBO) + SoC in reducing OCS use in adults with severe OCS-dependent asthma.

NAVIGATOR and PATHWAY both met their primary endpoint (annualised asthma exacerbation rate [AAER]) and demonstrated that tezepelumab 210 mg Q4W + SoC reduced the AAER by up to 71% and exacerbations leading to hospitalisation by up to 85% compared with PBO + SoC. (1, 8) Results from NAVIGATOR indicate that 0.85 patients need to be treated with tezepelumab 210 mg Q4W + SoC, instead of PBO Q4W + SoC alone, for one year in order to prevent an additional asthma exacerbation (i.e., the number needed to treat [NNT]).(9) The efficacy of tezepelumab 210 mg Q4W + SoC is supported across trials by clinically meaningful improvements in lung function, as measured by pre-bronchodilator (BD) forced expiratory volume in one second (FEV1), in addition to asthma control (Asthma Control Questionnaire 6-item [ACQ-6]), symptoms (Asthma Symptom Diary [ASD]) and HRQoL (Standardised Asthma Quality of Life Questionnaire for 12 years and older [AQLQ(S)+12] and St George's Respiratory Questionnaire [SGRQ]). (1, 7, 8, 10) Importantly, the efficacy of tezepelumab 210 mg Q4W + SoC was observed across the enrolled population of severe, uncontrolled asthma patients in all trials, irrespective of phenotypes and biomarkers, including in patients with EOS <150 cells/µL, for whom a particularly high unmet need exists due to the lack of available treatment options. (1, 7, 8, 10)

In SOURCE, 54.1% of patients treated with tezepelumab 210 mg Q4W + SoC achieved an OCS dose reduction of ≥90%, which was numerically greater than with PBO Q4W + SoC (46.1%). However, the primary endpoint of a categorised percent reduction in final daily OCS dose at Week 48 did not reach statistical significance. The proportion of patients treated with placebo who were able to reduce their OCS dose (i.e. placebo response) in this study was larger than observed in similar published studies of biologics.(11-13) This may be attributable to the unique SOURCE study design; a *post hoc* analysis of SOURCE results was performed in which OCS reduction phase duration and rules for

permission of multiple down-titration attempts were retrospectively altered to align with previous OCS-sparing studies. The *post hoc* analyses of categorised percent reduction in OCS dose resulted in a greater odds ratio (OR) in favour of tezepelumab 210 mg Q4W + SoC versus PBO Q4W + SoC that achieved statistical significance (OR: 2.16, 95% CI: 1.20, 3.89; nominal *p*=0.010).(14) The reduced exacerbation rate with tezepelumab compared with placebo observed across trials may result in a lower cumulative OCS dose; this may therefore prevent patients treated with tezepelumab from requiring long-term OCS use and becoming OCS-dependent. Accordingly, in a *post hoc* analysis of NAVIGATOR, patients treated with tezepelumab 210 mg Q4W + SoC had fewer exacerbations and, amongst those with exacerbations, fewer days of exacerbation-related systemic corticosteroid (SCS) use than patients who received PBO Q4W + SoC. Amongst patients who received OCS for exacerbations, patients treated with tezepelumab 210 mg + SoC received a lower total OCS dose than patients treated with PBO Q4W + SoC.(15) Tezepelumab has also been shown to be efficacious in OCS-dependent patients. Results from SOURCE and pooled results across NAVIGATOR and PATHWAY demonstrate the efficacy of tezepelumab in the subgroup of OCS-dependent patients for the majority of endpoints.(16-18)

Together, these trials demonstrate the favourable benefit/risk profile of tezepelumab in patients with severe, uncontrolled asthma, with no clinically meaningful differences in safety versus optimised SoC alone and no safety signals. (1, 7, 10)

4.2 Tezepelumab safety

Overall

Across the NAVIGATOR, PATHWAY and SOURCE trials, tezepelumab was well tolerated in patients with severe asthma and demonstrated a similar safety profile to optimised SoC alone. Furthermore, tezepelumab was associated with low discontinuation rates in patients with severe, uncontrolled asthma across phenotypes and irrespective of biomarkers.

AEs of special interest

Trial results show that the incidence of severe infections was low overall and similar between the tezepelumab 210 mg Q4W + SoC and PBO Q4W + SoC groups in NAVIGATOR (46 [8.7%] and 44 [8.3%] patients, respectively) and in PATHWAY (4 [2.9%] and 4 [2.9%], respectively). (7, 10) In SOURCE, the incidence of severe infections in the on-treatment period was lower in the tezepelumab 210 mg Q4W + SoC group (n=4 [5.4%]) than the PBO Q4W + SoC group (n=7 [9.2%]).(18) Furthermore, an in vitro study on human cells demonstrated that tezepelumab therapy improves host tolerance to viruses by decreasing inflammatory alarmins or cytokines without affecting anti-viral resistance.(19) The incidence of cancer did not differ between the treatment groups in NAVIGATOR (n=4 in both groups)(20) in SOURCE, there was one event of incidence of malignancy reported in the tezepelumab 210 mg Q4W + SoC group (1/74 [1.4%]) and no events in the PBO Q4W + SoC group. The event was not considered to be causally related to the treatment.(18)

4.3 Comparator and comparative efficacy

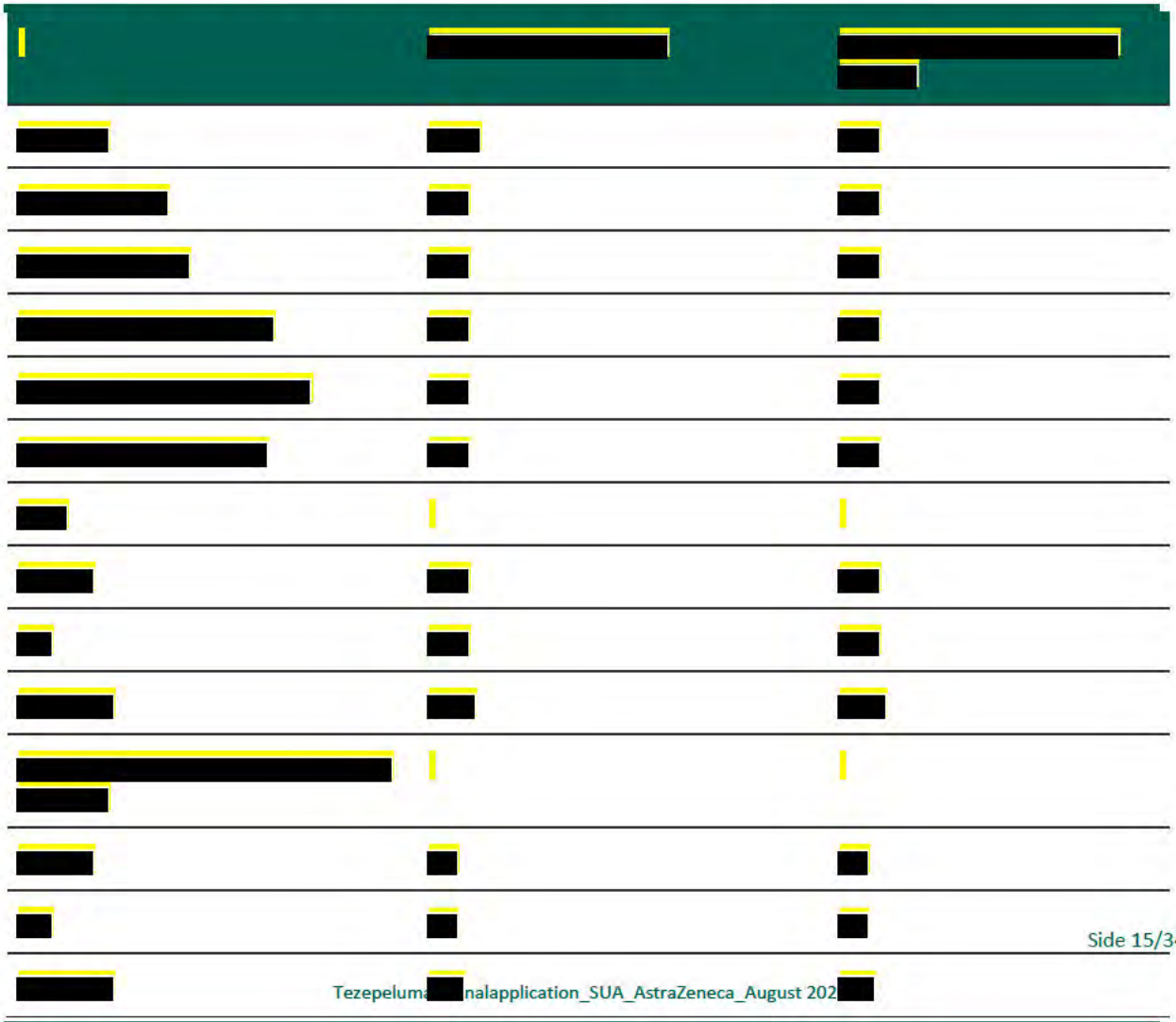
The included tezepelumab studies NAVIGATOR, PATHWAY and SOURCE all compare with SoC which is defined as medium to high-dose ICS and other maintenance treatment.

There are currently approved biologic treatments in asthma which are indicated for patients with severe disease; however, no head-to-head trials have compared the efficacy of tezepelumab with these biologics. ITC was therefore performed to compare tezepelumab with relevant biologics for the treatment of moderate-to-severe, uncontrolled asthma (covering the indications of approved biologics). (21, 22) Due to the complexity of trial comparisons (tezepelumab having a broader trial population than other biologics), a robust and exhaustive analysis has been developed. In indirect treatment comparisons (ITCs) with the other biologics, considering the outcomes of AAER and reduction in exacerbations leading to hospitalisation, tezepelumab 210 mg Q4W + SoC consistently demonstrated numerically favourable effectiveness compared to all comparators in the network meta-analysis (NMA). In terms of ACQ and FEV1, no clear clinical differences between biologics were observed in the NMA. Considering categorised percent reduction in OCS dose, although the results of the NMA favoured the other biologics, the NMA subgroup which offer more targeted comparisons, especially with respect to EOS-defined subgroups, suggested favourable effectiveness with tezepelumab.(22) A list of the biologic treatments included in the ITC is listed in Table 1.

AstraZeneca has analyzed the severe asthma treatment guideline made by the DMC with respect to identify comparators for this application. Overall, the DMC has deemed the clinical efficacy between dupilumab, benralizumab, mepolizumab, reslizumab and omalizumab to be comparable/equal where indications overlap. AstraZeneca has performed a network meta-analysis (NMA) confirming tezepelumab to also have a similar clinical efficacy compared to the other biologic therapies. Based on this, AstraZeneca regards dupilumab as the most relevant comparator to tezepelumab and dupilumab will therefore be the only biologic comparator in the health economic analysis. This is due to the broader trial population including both type 2 high asthma with EOS >150 and allergic asthma patients which is most similar to the indication of dupilumab.
Severe asthma is a heterogenous patient population. The DMC treatment guideline and clinical guidelines has therefore also been analysed to define the patient population in this application in accordance with current treatment initiation criteria, biomarker cut-offs etc used in Danish clinical practice. The definition of the patient populations which is used in both the medical section and the health economic section is therefore outlined below.

All patients in the tezepelumab studies are treated with medium-high dose ICS, have a min. of 2 exacerbations within a year and some patients are also treated with OCS. The inclusion of a medium-high dose ICS population is the same for the comparator studies (dupilumab) in the comparative analysis in this application. Furthermore, these patients are divided into subpopulations based on biomarker cut-offs according to Danish clinical practice:
***Type 2 high asthma**: EOS ≥150 AND/OR FeNO ≥25*
***Allergic asthma**: year-round allergy*
***Type 2 low asthma**: low EOS (<150) AND FeNO <25*
***High FeNO only**: FeNO ≥25 (is now included in the Type 2 high asthma according to the requested subpopulation)*

In the health economic analysis these subpopulations are further specified to only include high dose ICS (75% of the trial population). This is relevant to fit into the current DMC treatment guideline/clinical practice but also to only include patients within the EMA approved indication of tezepelumab. Patients with Type 2 high and allergic asthma have biologic treatments available today with recommendation from the DMC. However, type 2 low is not covered by current recommendation/indication of biologic treatments but could be covered by tezepelumab. The characteristics of the T2 low population used in the health economic analyses compared to the T2 low population in the full study population is illustrated in the table below. The cost effectiveness of tezepelumab is driven by the number of exacerbations in the subpopulations without biologic treatment today, why sensitivity analysis with more than 2 exacerbations are also presented for these subpopulations.



In the comparative efficacy analysis tezepelumab has demonstrated efficacy across phenotypes and irrespective of biomarkers, as evidenced by direct clinical evidence compared to SoC (GINA Step 4-5 treatment with medium-high dose ICS with another controller or maintenance OCS)(23), as well as comparable effectiveness with other biologics observed in the ITCs. This consolidates its positioning as the preferred first-line biologic across all patients with severe, uncontrolled asthma.

Table 1 Biologic treatments available

Biologic	Xolair®	Nucala®	Cinqaero®	Fasenra®	Dupixent®
Active	**Omalizumab**	**Mepolizumab**	**Reslizumab**	**Benralizumab**	**Dupilumab**
Company	Novartis	GlaxoSmithKline	Teva	AstraZeneca	Sanofi/Regeneron
Indicated phenotype	Allergic asthma	Eosinophilic asthma			Europe: type 2 inflammation (raised eosinophils and/or FeNO)
Mode of action	IgE antagonist that prevents binding of IgE to FcεRI (high-affinity IgE receptor), reducing the amount of free IgE available to trigger the allergic cascade and thereby decreasing multiple markers of airway inflammation, including EOS	IL-5 antagonist that blocks the binding of IL-5 to the α chain of the IL-5 receptor complex expressed on the EOS cell surface. This inhibits IL-5 signalling and leads to reduced production and survival of EOS	IL-5 antagonist that binds specifically to IL-5 and interferes with its binding to the IL-5 cell-surface receptor, thereby blocking its biological function and resulting in a reduction in the survival and activity of EOS	IL-5R antagonist, which induces depletion of EOS and basophils through enhanced antibody-dependent cell-mediated cytotoxicity; binds to EOS via IL-5Rα, blocking IL-5 binding to its receptor and therefore inhibiting IL-5 activity	IL-4R antagonist, which inhibits IL-4 and IL-13 signalling to reduce inflammation
Administration	SC incl. self admin.	SC incl. self admin.	IV infusion	SC incl. self admin. 30 mg Q4W (first three doses), followed by Q8W	SC incl. self admin.
Dose and frequency for adult patients	75–600 mg Q2W/Q4W (based on weight and baseline total serum IgE based)	100 mg Q4W	3 mg/kg Q4W		Initial dose of 600 mg, then 300 mg Q2W (or 400 mg, then 200 mg Q2W if patient does not require OCS)
Label indication					
EU	Xolair is indicated for adults and adolescents and children aged 6 years and older as add-on therapy to improve asthma control in patients with severe **persistent** allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and who have reduced lung	Nucala is indicated as an add-on treatment for severe **refractory** eosinophilic asthma in adults, adolescents and children aged 6 years and older	Cinqaero is indicated as add-on therapy in adult patients with severe eosinophilic asthma **inadequately controlled** despite high-dose inhaled corticosteroids plus another medicinal product for	Fasenra is indicated as an add-on maintenance treatment in adult patients with severe eosinophilic asthma **inadequately controlled** despite high-dose ICS+LABA	Dupixent is indicated in 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 FeNO, who are **inadequately controlled** with high-dose inhaled corticosteroid plus another

Biologic	Xolair®	Nucala®	Cinqaero®	Fasenra®	Dupixent®
	function (FEV_1 <80%) (adults and adolescents only) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus an inhaled LABA		maintenance treatment		medicinal product for maintenance treatment

Source: *SmPC for omalizumab, mepolizumab, reslizumab, benralizumab and dupilumab (24-28)*

4.4 Health economic analysis and results

All costs presented in this section is based on the AIP for tezepelumab. However, AstraZeneca will give a rebate that are competitive with the other recommended biologics.

Based on the NMA results, showing comparable efficacy for biologic therapies in severe uncontrolled asthma, AstraZeneca has conducted a cost-minimization analysis vs. dupilumab for the patient population with type 2 high asthma (including allergic asthma). The cost-minimization analysis showed an annual cost difference between tezepelumab and dupilumab of DKK 1 335 329 vs DKK 1 486 314. This result showed that tezepelumab could be cost-saving due to the higher frequency of administration with dupilumab and an initial loading dose.

The populations with type 2 low asthma have no access to biologic treatment today, thus cost-utility analyses were conducted with tezepelumab compared to SoC. The cost-utility analyses were based on the NAVIGATOR and SOURCE trials. The treatment cost for SoC was equal to high-dose ICS and LABA. The cost-utility analyses were based on a [redacted]

The results from the cost-utility analysis for the population with type 2 low asthma estimate a QALY gains of 0.474 and increase of cost with 711 297 DKK with treatment with tezepelumab compared to SoC. The ICER in this subpopulation is DKK 1 499 808 DKK.

Both deterministic and probabilistic sensitivity analyses were conducted for both sub-populations. The deterministic sensitivity analyses showed that the ICERs were sensitive to the number of exacerbations, which is expected since exacerbations are the main driver for the costs and health outcome, the ICERs were also sensitive to the drug acquisition costs for tezepelumab. The probabilistic sensitivity analyses showed that the majority of all 1,000 iterations were in the North-East quadrant indicating that tezepelumab is more effective and more costly in comparison to SoC in all iterations.

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

5.1 The medical condition and patient population

The pathophysiology of the disease and the clinical presentation/symptoms

Asthma is a chronic inflammatory disorder of the airways caused by the interaction of genetic and environmental factors. It is characterised by variable and reversible airflow obstruction, airflow inflammation, excessive mucus production and airway hyperresponsiveness that lead to recurrent episodes of wheezing, breathlessness, chest tightness and coughing.(29-31) Progressive pathologic airway remodelling may also occur, resulting in partially reversible or irreversible airway obstruction.(31) Severe asthma is a heterogeneous syndrome encompassing several clinical phenotypes that differs according to age of onset of asthma, presence or absence of allergy, severity of airflow limitation, frequency of exacerbations, response to treatment and prognosis and is associated with a reduced quality of life, exacerbations, increased health care resource use, hospitalization and death. (32, 33)

Even though these patients often require repetitive glucocorticoid bursts, maintenance oral glucocorticoid therapy on top of adequate treatment with high dose inhaled glucocorticoids, LABA and LAMA, disease control is not obtained as some patients still experience persistent symptoms and frequent exacerbations.(29)

In Denmark it is estimated that approximately 7-11% of the Danish population are suffering of asthma.(34) The prevalence of severe asthma is 5-15% of asthma patients and approximately half (50%) of these patients have type 2-inflammation (T2 inflammation), which is categorized by production of cytokines IL-4, IL-5, IL-13, IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) initiated by either the adaptive or the innate immune system. (35, 36) T2 inflammation can be initiated by allergens, virus, bacteria, and irritants. T2 inflammation is often characterized by increased level of eosinophiles (EOS) in the blood and/or increased fractional exhaled nitric oxide FeNO and/or allergic asthma with IgE-sensitization for allergens demonstrated by measuring of increased level of specific IgE in the blood or by skin prick test.(36)

Type 2 high inflammation (T2 high) is characterized by eosinophilic airway inflammation, where increased blood eosinophil counts and/or elevations of FeNO often can be measured. Type 2 low inflammation (T2 low) can beside lower levels of Type 2 high inflammation also be characterized by neutrophilic asthma and/or paucigranulocytic asthma.(32)

Current treatment option(s)

(the section below is based on the DMC treatment guideline and the protocol for assessment of dupilumab)

The Danish Respiratory Society (DLS) defines severe asthma in accordance with ERS (European Respiratory Society)/ATS (American Thoracic Society) guidelines as: asthma which for at least the last year, has required high dose inhalation steroid treatment as well as one or more additional treatments (2nd controller (typically long-acting beta2-agonist, LABA) and/or who have required perorally steroid (OCS) for ≥ 50% of the time) to prevent asthma from becoming uncontrolled or, despite this treatment, remains uncontrolled. (35, 37) Systematic examination of possible severe asthma is essential to ensure diagnosis and that the lack of disease control is not due to incorrect diagnosis, lack of adherence with the prescribed treatment, treatable comorbidities, or avoidable triggers.7 However, there is a smaller proportion of patients who do not achieve adequate disease control despite the above measures. For patients with severe eosinophilic asthma, an additional biologic treatment option is available with mepolizumab, reslizumab, dupilumab or benralizumab, which are antibodies targeting interleukin 5 (IL-5), anti-IL4Ra or IL-5 receptor (IL-5R). Mepolizumab is approved by the EMA for adults and children over 6 years of age.(25) Reslizumab and benralizumab are approved for adults. (26, 27) IL-5 is a cytokine that plays a key role in the production, maturation, and survival of eosinophilic granulocytes, and binding the antibodies to IL-5 or IL-5R thus leads to a reduction in the number of eosinophilic granulocytes, resulting in better disease control. In adult patients and children over 6 years of age with severe allergic asthma who have a positive skin prick test or in vitro reactivity for a year-round airborne

allergen/perennial allergy, a treatment option is additional therapy with anti-IgE treatment in the form of omalizumab or dupilumab. Omalizumab is an antibody aimed at IgE which prevents the binding of IgE to immune system cells, thereby reducing allergic reactions.(24) Lastly dupilumab is an antibody targeting IL-4Ra and is also used for patients from the age of 12, with both high eosinophilic asthma and for patients with severe allergic asthma.(28) In the current treatment guideline from the DMC, patients with severe uncontrolled asthma can be offered treatment with one of the biologics if they meet the following criteria:

- Systematic investigation of possible severe asthma has been carried out, according to DLS guidelines.
- Treatment steps similar to severe asthma in the previous year according to ERS/ATS guidelines, i.e. combination therapy with high-dose ICS as well as one or more additional treatments and/or fixed treatment with OCS.
- Lack of response defined by ≥ 2 annual exacerbations or daily maintenance therapy with OCS at a dose of ≥ 5 mg prednisolone equivalent for more than 50 % of the time in the previous year.

The IgE, EOS and FeNO biomarkers are currently used to define different subtypes of asthma, as they are indicative of distinct inflammatory pathways; these are central to the management of severe, uncontrolled asthma, as biologic treatments are prescribed on the basis of individual inflammatory pathways in current clinical practice.(2, 6, 38) However most severe, uncontrolled asthma patients are positive for one or two of these key biomarkers, but relatively few patients are either positive or negative for all three of these biomarkers. (39-42) This can indicate either the upregulation of multiple key inflammatory pathways or a lack of upregulation of these pathways, Therefore, it is often unclear if a patient has an allergic phenotype, an eosinophilic phenotype or neither phenotype.(2) Further, there is no biologic therapy available for patients with severe uncontrolled T2 low inflammation asthma.

Patient-numbers

[redacted]

In 2019 the expert committee for severe asthma in the DMC estimated the prevalence and incidence of severe asthma patients eligible for treatment with biologics in their protocol for the assessment of dupilumab.
Their estimate was a prevalence of 500-600 patients (Type 2 high including allergic asthma) with 60 new patients every year. It was also stated that the distribution of Type 2 high (EOS ≥150), allergic and FeNO only is 70%, 30% and 3%. Based on this estimate the total eligible number of patients in 2022 and 2023 is 780 and 840 for patients with Type 2 high inflammation (high EOS) including allergy. The expert committee has not estimated the number of Type 2 low asthma, but in NAVIGATOR 13% of patients had EOS <150 and FeNO <25 among the population who received high dose ICS (see baseline characteristics for more details in later sections).
This % is used to estimate the Danish population size of the Type 2 low, Table 2 below, as this is the number of patients who are just as severely affected and burdened with symptoms by their asthma as is it is required for treatment initiation with biologics in guidelines today, despite not reaching the biomarker cut-offs of EOS ≥150. This means that in calculations below, an additional 13% of total severe asthma patients eligible for treatment with biologics is added to the total patient population. The 3% FeNO only patients, is also added on top of the estimated patient number by the DMC in 2019.

The incidence and prevalence estimates made by the expert committee in the DMC is also used as basis to calculate the prevalence and incidence in the past 5 years and 5 years ahead are shown in Table 2 and 3.

Table 2 Incidence and prevalence in the past 5 years

Year	2017	2018	2019	2020	2021
Incidence in Denmark (T2 high/Allergic/T2 low/FeNO only)	70 (42/18/8/2)	70 (42/18/8/2)	70 (42/18/8/2)	70 (42/18/8/2)	70 (42/18/8/2)
Prevalent T2 high (EOS ≥150 and/ orhigh FeNO) adult patients and adolescents ≥12 years on January 1st	336	378	420	462	504
Prevalent allergic adult patients and adolescents ≥12 years on January 1st	144	162	180	198	216
Prevalent T2 low adult patients and adolescents ≥12 years on January 1st	62	70	78	86	94
Prevalent FeNO only adult patients and adolescents ≥12 years on January 1st	14	16	18	20	22

Table 3 The incidence and prevalence 5 years ahead

Year	2022	2023	2024	2025	2026
Incidence in Denmark (T2 high/Allergic/T2low/ FeNO only)	70 (42/18/8/2)	70 (42/18/8/2)	70 (42/18/8/2)	70 (42/18/8/2)	70 (42/18/8/2)
Prevalent T2 high (EOS ≥150 and/or high FeNO) adult patients and adolescents ≥12 years on January 1st	546	588	630	672	714
Prevalent allergic adult patients and adolescents ≥12 years on January 1st	234	252	270	288	306
Prevalent T2 low adult patients and adolescents ≥12 years on January 1st	101	109	117	125	133
Prevalent FeNO only adult patients and adolescents ≥12 years on January 1st	23	25	27	29	31

Even though all patients estimated in the Table 2 and 3 above are considered eligible for tezepelumab, many of these patients are already on biologic treatment. The expected patient numbers after recommendation is therefore different and stated below and in Table 4.

[redacted] Some of these patients could switch to tezepelumab after recommendation. However, switches are not included in the estimate of new patients in Table 4.

Besides switches the patient numbers are also difficult to predict as uptake of these products are regulated by price and a tender. So, the assumptions used for the estimated patient numbers in Table 4 below are:

- Tezepelumab can be available from late November 2022. Patient in 2022 are estimated to be non/low as it is uncertain when the recommendation from the DMC is ready.
- Patient numbers from 2023-2026 are estimated based on a positive assessment by DMC and based on the full indication. These are primarily the incident population after year 2023, as a large proportion of the prevalent population are already treated with the other biologics. In 2023 the number of eligible patients will mostly be prevalent Type 2 low patients and High FeNO only patients as these patients do not currently have a treatment option. A small proportion of the prevalent Type 2 high and allergic patients will switch from current treatment, due to treatment discontinuation, and some of these patients may therefore switch to tezepelumab.
- The class of biologics is subject to tenders. We have not included any assumptions around the positioning of tezepelumab in these tenders. The positioning in the tender/treatment guideline will be important as this dictates a 80/20% split of the tender winner versus the others.

In the estimation below it is assumed that all Type 2 low, High FeNO only patients plus half of the incident Type 2 high and allergic population will get treated with tezepelumab after recommendation. It is optimistic to think that all prevalent Type 2 low patients and High FeNO patients will be referred for evaluation of treatment with a biologic in 2023, which is why the uptake is assumed to be slower and distributed from 2023-2026 below.

Table 4 Estimated number of new patients eligible for treatment per year

	2022	2023	2024	2025	2026
Number of new patients in Denmark who are expected to use the pharmaceutical in the coming years	0	62	62	62	62
T2 high (EOS ≥150 and/or high FeNO) adult patients and adolescents ≥12 years	0	21	21	21	21
Allergic adult patients and adolescents ≥12 years	0	9	9	9	9
T2 low adult patients and adolescents ≥12 years	0	32	32	32	32
FeNO only adult patients and adolescents ≥12 years (now included in the EOS ≥150 and/or FeNO)	0	0	0	0	0
Total number of patients (accumulative)	0	62	124	186	248

5.1.1 Patient populations relevant for this application

Current biologics assessed by the DMC are targeting the severe uncontrolled eosinophilic asthma patient and the allergic patients with and without co-expression of other biomarkers. Tezepelumab can also treat these patients, however tezepelumab can also treat the ones which is not sufficiently treated with current biologic treatment (switch) and patients not eligible for treatment due to low or no expression of T2 inflammatory biomarkers or co-expression of two or more biomarkers. Which means:

The patients who have either low and high biomarker status including patients with multiple inflammatory drivers having high symptomatic disease burden despite the availability of existing biologics and would benefit from a novel treatment with an upstream MOA, meaning:

- Bio-naïve severe asthma patients regardless of biomarker levels or dominance
- Switch patients regardless of phenotype not achieving treatment targets on current biologic and switching to a new MoA
- The Type 2 low symptomatic uncontrolled asthma patient characteristics which embraces the absence or low presence of T2 markers meaning low FeNO, low EOS, adult-onset and diagnosis of asthma and may be allergic, poor response to but high use of SABA, not responding sufficiently to ICS or OCS.

Importantly this is also aligned with the new updated version of GINA 2022 recommendations. (23)

In conclusion this covers the whole patient population estimated in the section above. However as was also mentioned above, there are currently other biologic treatments and a tender that decides the treatment split. It is expected that tezepelumab will get a proportion of new patients (incident population), and switch patients (prevalent population) depending on the tender outcome both within high EOS and high FeNO, high EOS only and allergic patients with or without co-expression of FeNO or EOS. For the patients with Type 2 low and High FeNO only asthma tezepelumab will be the first biologic treatment and the whole population is therefore relevant for this application.
An overview of the patient population treated with tezepelumab in the NAVIGATOR trial can be seen in the Venn diagram in figure 1 below. This illustrates the effect of tezepelumab irrespective of biomarkers.

Figure 1 Overview of biomarker expression in the NAVIGATOR trial

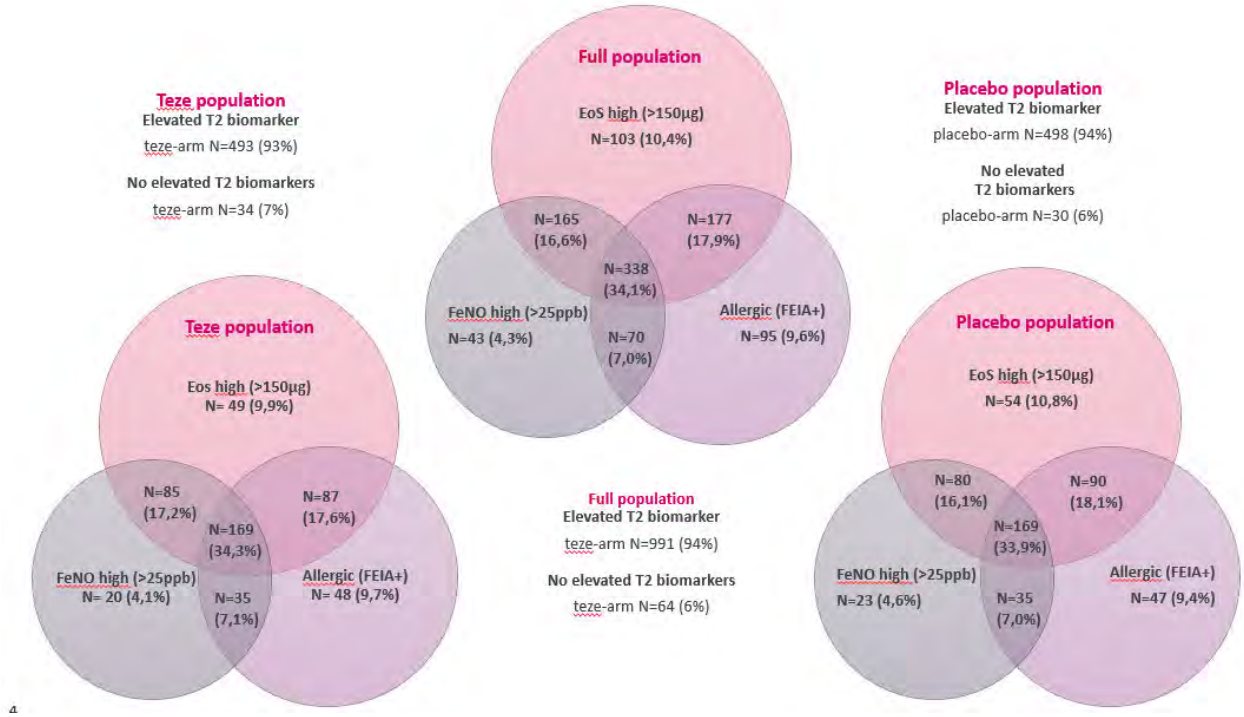


Figure 1 is based on NAVIGATOR data, which includes both medium and high dose ICS, which is why these numbers deviates from the estimated patient population in the section above (which is only based on high dose ICS). For more detail se baseline characteristics in later sections.

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

The Danish Respiratory Society (DLS) defines severe asthma in accordance with ERS (European Respiratory Society)/ATS (American Thoracic Society) guidelines: asthma which for at least the last year has required high dose inhalation steroid treatment as well as one or more additional treatments (2nd controller (typically long-acting beta2-agonist, LABA) and/or who have required perorally steroid (OCS) for ≥ 50% of the time) to prevent asthma from becoming uncontrolled or, despite this treatment, remains uncontrolled. (35, 37) Systematic examination of possible severe asthma is essential to ensure diagnosis and that the lack of disease control is not due to incorrect diagnosis, lack of adherence with the prescribed treatment, treatable comorbidities, or avoidable triggers.(37) However, there is a smaller proportion of patients who do not achieve adequate disease control despite the above measures. Some of these patients can be offered biologic treatment. Patients with severe eosinophilic asthma, can today be treated with mepolizumab, reslizumab or benralizumab, which are antibodies targeting interleukin 5 (IL-5) or IL-5 receptor (IL-5R). Mepolizumab is approved by the EMA for adults and children over 6 years of age. (25) Reslizumab and benralizumab are approved for adults.(26, 27) IL-5 is a cytokine that plays a key role in the production, maturation, and survival of eosinophilic granulocytes, and binding the antibodies to IL-5 or IL-5R thus leads to a reduction in the number of eosinophilic granulocytes, resulting in better disease control. In adult patients and children over 6 years of age with severe allergic asthma who have a positive skin prick test or in vitro reactivity for a year-round airborne allergen/perennial allergy, a treatment option is additional therapy with anti-IgE treatment in the form of omalizumab or dupilumab. Omalizumab is an antibody aimed at IgE which prevents the binding of IgE to immune system cells, thereby reducing allergic

reactions. (37) Lastly dupilumab is an antibody targeting IL-4Ra and is also used for patients aged ≥12 with both eosinophilic asthma and for patients with severe allergic asthma. (44)

The IgE, EOS and FeNO biomarkers are currently used to define different subtypes of asthma, as they are indicative of distinct inflammatory pathways; these are central to the management of severe, uncontrolled asthma, as biologic treatments are prescribed on the basis of individual inflammatory pathways in current clinical practice. (34-36, 42) However, most severe, uncontrolled asthma patients are positive for one or two of these key biomarkers, but relatively few patients are either positive or negative for all three of these biomarkers. This can indicate either the upregulation of multiple key inflammatory pathways or a lack of upregulation of these pathways, Therefore, it is often unclear if a patient has an allergic phenotype, an eosinophilic phenotype or neither phenotype.(34) [redacted] In the latest version of the 2022 GINA recommendation tezepelumab has been added for patients > 12 who have no evidence of type 2 inflammation (T2 low) on repeated testing. (23) [redacted] In Figure 1, it shows that the HCRU was similar in both groups. In A) non-Type 2 low is defined as EOS>150 and FeNO>25, while Type 2 low is defined as EOS<150 and FeNO<25.

[redacted]

5.2.2 Choice of comparator(s)

Tezepelumab has a wider indication than any other biologic treatment. Furthermore current biologics are subscribed based on presence of specific biomarkers at a predefined biomarker cutoff. The rationale for choice of comparators in the different subpopulations is therefore outlined below.

For patients with evidence of allergic or eosinophilic asthma, there are five currently indicated and reimbursed biologic therapies that are used in Danish clinical practice (dupilumab, benralizumab, mepolizumab, reslizumab and omalizumab).

Overall, the DMC has deemed the clinical efficacy between the other biologic treatments: dupilumab, benralizumab, mepolizumab and reslizumab to be comparable for severe eosinophilic asthma. For severe allergic asthma the DMC has also deemed dupilumab and omalizumab as clinically equal. AstraZeneca has performed a network meta-analysis (NMA) confirming tezepelumab to also have a similar clinical efficacy as the other biologics (presented in section 6 according to template). The overall results from the NMA will be presented for all biologics, however only dupilumab will be covered in detail as the main comparator for allergic and eosinophilic asthma due to the largest overlap in potential populations (by indication and in clinical practice).

However, the indication for tezepelumab is broader than the comparators, and can also cover patients with Type 2 low inflammation asthma. Thus, AstraZeneca regards high-dose ICS/LABA (± other controller medications) as the relevant comparator in this segment in alignment with current standard of care for this population. The same comparators will be used in the health economic section.

5.2.3 Description of the comparator(s)

High-dose ICS/LABA ± other controller medication is the comparator for the patients not currently eligible for biologic treatment (Type 2 low asthma subgroup and High FeNO only) is in alignment with the SoC arm in tezepelumab trials, PATHWAY: medium-to-high dose ICS+LABA (± other controller medications), NAVIGATOR: medium-to-high dose ICS + ≥1 other controller medication and SOURCE: High-dose ICS+LABA + OCS (to be tapered down) ± other controller medications. Medium to high dose was defined as daily dose of ≥500 µg of fluticasone propionate or equivalent in the tezepelumab trials.

A description of the comparators for the remaining currently biologic eligible population (severe Type 2 high including allergic asthma) can be seen in the Table 5 below. The main comparator is dupixent.

Table 5 Description of all five biologic comparators

Comparator	Dupixent	Nucala	Fasenra	Xolair	Cinqaero
Generic Name (ATC-code):	Dupilumab (D11AH05)	Mepolizumab (R03DX09)	Benralizumab (R03DX10)	Omalizumab (R03DX05)	Reslizumab (R03DX08)
Mode of action:	Dupilumab is a fully human monoclonal antibody against interleukin (IL)-4 receptor alpha that	Mepolizumab is a humanised monoclonal antibody (IgG1, kappa), which	Benralizumab is an anti-eosinophil, humanised afucosylated, monoclonal	Omalizumab binds to IgE and prevents binding of IgE to FceRI (high-affinity IgE receptor) on	Reslizumab is a humanised monoclonal antibody (IgG4, κ) against the

	inhibits IL-4/IL-13 signalling	targets human interleukin-5 (IL-5) with high affinity and specificity.	antibody (IgG1, kappa). It binds to the alpha subunit of the human interleukin-5 receptor (IL-5Rα) with high affinity and specificity.	basophils and mast cells, thereby reducing the amount of free IgE that is available to trigger the allergic cascade.	human interleukin-5 (IL-5). Reslizumab binds specifically to IL-5 and interferes with IL-5 binding to its cell-surface receptor.
Pharmaceutical form:	Solution for injection or prefilled pen	Solution for injection or prefilled pen	Solution for injection or prefilled pen	Powder and solvent for solution for injection.	Concentrate for solution for infusion (sterile concentrate)
Posology and dosing:	For patients with severe asthma and who are on oral corticosteroids or for patients with severe asthma and co-morbid moderate-to-severe atopic dermatitis or adults with co-morbid severe chronic rhinosinusitis with nasal polyposis, an initial dose of 600 mg (two 300 mg injections), followed by 300 mg every other week administered as subcutaneous injection. For all other patients, an initial dose of 400 mg (two 200 mg injections), followed by 200 mg every other week administered as	For severe eosinophilic asthma Adults and adolescents aged 12 years and over The recommended dose of mepolizumab is 100 mg administered subcutaneously once every 4 weeks. Children aged 6 to 11 years old Nucala 100 mg solution for injection in pre-filled pen and Nucala 100 mg solution for injection in prefilled syringe are not indicated for administration to this population. The powder for solution for injection presentation is appropriate for administration to this population. The recommended dose	The recommended dose of benralizumab is 30 mg by subcutaneous injection every 4 weeks for the first 3 doses, and then every 8 weeks thereafter. If an injection is missed on the planned date, dosing should resume as soon as possible on the indicated regimen; a double dose must not be administered. It should be injected into the thigh or abdomen. If the healthcare professional or caregiver administers the injection, the upper arm can also be used. It should not be injected into	The appropriate dose and frequency of Xolair for these conditions 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 Xolair in 1 to 4 injections may be needed for each administration. The maximum recommended dose is 600 mg	Is given as intravenous infusion once every four weeks. Patients below 35 kg or above 199 kg The recommended dose is 3 mg/kg body weight. The volume (in mL) required from the vial(s) should be calculated as follows: 0.3 x patient body weight (in kg). Patients between 35 kg and 199 kg: The recommended dose is achieved using the vial-based dosing scheme. The recommended dose is based on patient body weight and should only be

	subcutaneous injection. Patients receiving concomitant oral corticosteroids may reduce their steroid dose once clinical improvement with dupilumab has occurred (see section 5.1). Steroid reductions should be accomplished gradually. 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. Method of administration: Dupilumab is administered by subcutaneous injection into the thigh or abdomen, except for the 5 cm around the navel. If somebody else administers the injection, the upper arm can also be used.	of mepolizumab is 40 mg administered subcutaneously once every 4 weeks. The pre-filled pen or pre-filled syringe should be used for subcutaneous injection only. or self-administration the recommended injection sites are the abdomen or thigh. A caregiver can also inject Nucala into the upper arm. For doses which require more than one injection, it is recommended that each injection is administered at least 5 cm apart.	areas where the skin is tender, bruised, erythematous, or hardened.	omalizumab every two weeks. For subcutaneous administration only. Xolair must not be administered by the intravenous or intramuscular route. Doses of more than 150 mg should be divided across two or more injection sites. There is limited experience with self-administration of Xolair powder and solvent for solution for injection. Therefore, treatment with this formulation is intended to be administered by a healthcare provider only.	adjusted for significant changes in body weight. This medicinal product is for intravenous infusion only. It must not be administered by the subcutaneous, oral or intramuscular route. The appropriate volume of concentrate should be dispensed into an infusion bag containing 50 mL sodium chloride 9 mg/mL (0.9%) solution for infusion.

Should the pharmaceutical be administered with other medicines?	No however dupilumab is indicated 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).	No however mepolizumab is indicated as an add-on treatment for severe refractory eosinophilic asthma.	No however benralizumab is indicated as an add-on treatment for severe eosinophilic asthma.	No however omalizumab is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma.	No however reslizumab is an add-on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment
Treatment duration/criteria for end of treatment:	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.	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 disease severity and level of control of exacerbations.	Fasenra is intended for long-term treatment. A decision to continue the therapy should be made at least annually based on disease severity, level of exacerbation control and blood eosinophil counts.	Is intended for long-term treatment. Clinical trials have demonstrated that it takes at least 12-16 weeks for Xolair treatment to show effectiveness	Is intended for long-term treatment. A decision to continue the therapy should be made at least annually based on disease severity and level of exacerbation control.
Necessary monitoring, both during administration and during the treatment period:	No	No	No	No	No
Need for diagnostics or other tests:	No except for eosinophil count(blood test)	No except for eosinophil count(blood test)	No except for eosinophil count(blood test)	A positive skin test or in vitro reactivity to a perennial aeroallergen.	No except for eosinophil count(blood/sputum test)

Packaging	Pack of 200 mg or 300 mg with 2 syringes/pen.	Pack of 1 or 3 100 mg syringes/pen.	Pack of 1 30 mg syringe/pen	Pack of 75 or 150 mg with 1 syringe	10 ml or 2,5 ml pack of 10 mg/ml vials

5.2.4 The intervention

From the broader pool of the total asthma population, there is a smaller proportion of patients, that despite systematic examination and treatment do not achieve adequate disease control despite available treatments.
Tezepelumab represents a new class of biologic (anti-TSLP) in the treatment of severe, uncontrolled asthma, blocking TSLP at the top of the inflammatory cascade and interfering with multiple downstream inflammatory pathways to deliver efficacy across phenotypes and irrespective of biomarkers, including allergic, non-allergic, EOS-high and -low, and FeNO high and low populations.

Tezspire

Generic name (ATC-code):

Tezepelumab (R03DX11)

Mode of action:

- Tezepelumab blocks the action of thymic stromal lymphopoietin (TSLP), an epithelial cytokine that plays a key role across the spectrum of asthma inflammation

Pharmaceutical form:

- Solution for injection. Pre-filled syringe contains 210 mg tezepelumab in 1.91 mL solution (110 mg/mL)

Posology/expected indication and dosing:

Tezspire is indicated as an add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma who are inadequately controlled with medium to high dose inhaled corticosteroids plus another medicinal product for maintenance treatment

Adults and adolescents (aged 12 years and older): The recommended dose is 210 mg of tezepelumab by subcutaneous injection every 4 weeks. No loading dose is required

Should the pharmaceutical be administered with other medicines?

- No but there will for most patients also be a background treatment

Treatment duration/criteria for end of treatment:

- Tezspire 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.

Necessary monitoring, both during administration and during the treatment period:

- No

Need for diagnostics or other tests:

- No except for eosinophil count(blood test)

Packaging/storage/shelf life:

- Pack of 210 mg with on syringe. Store in a refrigerator (2°C - 8°C). Tezspire may be kept at room temperature (20°C - 25°C) for a maximum of 30 days. After removal from the refrigerator. Shelf life is 3 years.

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

Due to the lack of head-to-head trials investigating tezepelumab compared to other biologic treatments identified as relevant comparators to tezepelumab, a clinical systematic literature review (SLR) was conducted. In the SLR, RCTs that assessed the efficacy and safety of tezepelumab, benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab in adult and adolescent patients with moderate-to-severe, uncontrolled asthma were identified. RCTs using approved dosages of the comparator biologics (based on prescribing information from the FDA, EMA and PMDA) were included. The use of GINA Step 4/5 therapies was used as a inclusion criteria, thus studies reported LABA use (in combination with at least medium dose ICS) among at least 75% of the enrolled patients were included in the SLR. Relevant studies identified through the SLR were included in the evidence base that formed the basis of the subsequently conducted ITCs. (21, 22)

The PICOS (ie, population, intervention, comparator, outcome, and study design) criteria for the SLR are presented in Table 6 below.

Table 6 PICOS criteria for the systematic literature review

	Inclusion criteria	Exclusion criteria
Population	• Patients at least 12 years of age who have asthma that remains uncontrolled despite adherence with maximal optimized GINA Step 4 or 5 treatment, including medium to high dose ICS and LABA[a]	Mild disease severity only Other respiratory disease without asthma included Non-human studies • All patients under the age of 12
Interventions/ Comparators	• Tezepelumab (210 mg every four weeks) **Approved dosages of the following based on prescribing information from FDA, EMA, and/or Japan[b]:** Anti-IgE • Omalizumab (75 to 375 mg [FDA and Japan] or 600 mg [EMA] every 2 or 4 weeks; dose and frequency determined by baseline IgE level and body weight [kg])(46); (47) Anti-IL-5 • Mepolizumab (100 mg every 4 weeks)(48); • Reslizumab (3 mg/kg once every 4 weeks)(49); • Benralizumab (30 mg every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter)(50); Anti-IL-4/IL-13 • Dupilumab (An initial dose of 400 mg [two 200 mg injections] followed by 200 mg given every other week	Other treatments not listed in inclusion criteria Treatments or doses not indicated/approved for the population of interest Non-pharmacological interventions

	Inclusion criteria	Exclusion criteria
	or an initial dose of 600 mg [two 300 mg injections] followed by 300 mg given every other week)(51);	
Outcomes	Efficacy, safety, and patient-reported outcomes including (but not limited to): 1. Exacerbation rate reduction 2. Exacerbations leading to hospital/ER visits 3. Reduction in OCS use 4. Improvements in quality of life (e.g., generic measures such as EQ-5D and SF-36, and disease specific measures such as AQLQ, SGRQ, cough assessments, and impact specific PROs) 5. Response to treatment 6. Discontinuation of treatment 7. Reduction in biomarkers (e.g., blood eosinophils, IgE, FeNO)	• NA (not excluding based on outcomes)
Study design	• RCTs reported in peer-reviewed publications, conference abstracts/posters, or grey literature • Systematic reviews, meta-analyses, and network meta-analyses [c]	• Non-RCTs • Single-arm studies • Study protocols • Opinion pieces, commentaries, letters, editorials, case reports • Economic/cost-effectiveness evaluations • Narrative reviews (ie, non-systematic) • Pooled analyses of RCTs • Subgroup analyses not of interest
Study language	• English [d]	• Non-English
Date restrictions	• No restriction: From the inception of the databases to date of search; additionally, regular alerts will be established	• None
Geographic location	• Global	• None

[a] This criterion was relaxed after initial screening to permit inclusion of studies in which at least 75% of patients reported LABA use (plus at least medium dose ICS), despite not requiring use of LABA or other controllers as a part of their inclusion criteria
[b] Latest version of Japan prescribing information (as for March 2020)
[c] Systematic reviews, meta-analyses, network meta-analyses, and the bibliographies of these records were reviewed and cross-referenced with the included study lists to ensure that no primary studies were missed.
[d] Search captured all languages, but non-English citations were excluded during full-text screening.
Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; EMA = European Medicines Agency; ER = emergency room; EQ-5D = EuroQol-5 Dimensions; FDA = Food and Drug Administration; FeNO = fractional exhaled nitric oxide; ICS = inhaled corticosteroid; IgE = immunoglobulin E; IL = interleukin; kg = kilogram; LABA = Long-Acting β-Agonist; mg = milligram; PRO = patient reported outcome; RCT = randomized controlled trial; SF-36 = 36-Item Short Form Health Survey; SGRQ = St. George's Respiratory Questionnaire.

The SLR adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance and included a comprehensive database search as well as a targeted grey literature search and hand search. (52) MEDLINE®, EMBASE, and the Cochrane Central Register of Controlled Trials were searched by an experienced information specialist and peer-reviewed by a second information specialist. The search was conducted on October 2020 and updated in January 2022. Various supplemental searches were also conducted including clinical trial registries, relevant conferences, and websites for multiple health technology assessment (HTA) and regulatory agencies. Among the 41 RCTs identified from both the original and the update SLR, four were not included in the ITCs because they did not report any of the main outcomes of interest. Thus, 37 RCTs were included in the ITCs. Additional subgroup data (triple-positive patients) from the NAVIGATOR trial was provided by AstraZeneca during the update, and was also included in the ITC. The result of the NMA for all biologic treatments will be presented here, however only tezepelumab and dupilumab will be described in more detail here, as dupilumab is the main biologic comparator for tezepelumab. Therefore, the selected

studies for tezepelumab and dupilumab will be described in the sections below and in appendix according to the template. The full lists of RCTs, characteristics, comparisons etc. is shared in the appendix and full NMA report.

6.2 List of relevant studies

Table 7 Relevant studies included in the assessment (tezepelumab and dupilumab) – for more details see Appendix B

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
Included: *Corren*, Jonathan et al. "Tezepelumab in Adults with Uncontrolled Asthma." *The New England journal of medicine* vol. 377,10 (2017): 936-946.	PATHWAY	NCT02054130	13. December 2013 01. marts 2017	Tezepelumab 70 mg SC Q4W (low dose; 138 patients), Tezepelumab 210 mg SC Q4W (medium dose; 137 patients), Tezepelumab 280 mg SC Q2W (high dose; 137 patients)
Included: Menzies-Gow, Andrew et al. "Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma." The New England journal of medicine vol. 384,19 (2021): 1800-1809.	NAVIGATOR	NCT03347279	23. November 2017 12. November 2020	Tezepelumab 210 mg Q4W subcutaneously or placebo Q4W for 48 weeks.
Included: Wechsler ME et. Al.: a phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy and safety of tezepelumab in reducing oral corticosteroid use in adults with oral corticosteroid dependent asthma.	SOURCE	NCT03406078	05. March 2018 25. September 2020	Tezepelumab subcutaneous injection vs Placebo subcutaneous injection

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
Respir Res. 2020 Oct 13;21(1):264				
Included: Wenzel S et al Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial		NCT01854047	June 2013 April 2015	24-week of subcutaneous dupilumab 200 mg or 300 mg every 2 weeks or every 4 weeks, or placebo
Included Busse WW et al Liberty Asthma QUEST: Phase 3 Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate Dupilumab Efficacy/Safety in Patients with Uncontrolled, Moderate-to-Severe Asthma	LIBERTY ASTHMA QUEST	NCT02414854	April 27, 2015 July 29, 2017	52 weeks of subcutaneously administered dupilumab 200 or 300 mg every 2 weeks or placebo
Included: Rabe K et al Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma	LIBERTY ASTHMA VENTURE	NCT02528214	Oct 15 2015 Sep 20 2017	24 weeks of 300 mg every 2 weeks or placebo
Included: Wechsler et al A Randomized, Double-blind, Placebo-controlled, Parallel-group, 12-week Proof-of-Concept (PoC) Study to Assess the Efficacy, Safety, and Tolerability		NCT03387852	March 12, 2018 August 7, 2019	20 weeks of 300 mg Q2W and/or placebo and/or SAR440340

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
of SAR440340 and the Coadministration of SAR440340 and Dupilumab in Patients With Moderate-to-Severe Asthma Who Are Not Well Controlled on Inhaled Corticosteroid (ICS) Plus Long-acting β2 Adrenergic Agonist (LABA) Therapy				
Included: Wechsler M et al Long-Term Safety Evaluation of Dupilumab in Patients With Asthma	LIBERTY ASTHMA TRAVERSE	NCT02134028	Apr 30 2014 Oct 11 2019	Up to 96 weeks dupilumab 300 mg every 2 weeks, open-label extension

Table 8 Tezepelumab studies not included in the assessment (other excluded studies are described in Appendix B)

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
Not included/results not yet completed: Bowen K, Hellqvist Å, Colice G: a phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the long-term safety and tolerability of tezepelumab in adults and adolescents with severe, uncontrolled asthma. Respir Res. 2020 Oct 21;21(1):279	DESTINATION	NCT03706079	January 7, 2019 May 20, 2022	Tezepelumab subcutaneous injection vs Placebo subcutaneous injection

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
Not Included: Menzies-Gow A, Wechsler ME et. al. Effect of tezepelumab on airway inflammatory cells, remodelling, and hyperresponsiveness in patients with moderate-to-severe uncontrolled asthma (CASCADE): a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet Respir Med. 2021 Nov;9(11):1299-1312. Epub 2021 Jul 10. Erratum in: Lancet Respir Med. 2021 Nov;9(11):	CASCADE	NCT03688074	02. November , 2018 16. November, 2020	Tezepelumab subcutaneous injection vs Placebo subcutaneous injection

7. Efficacy and safety

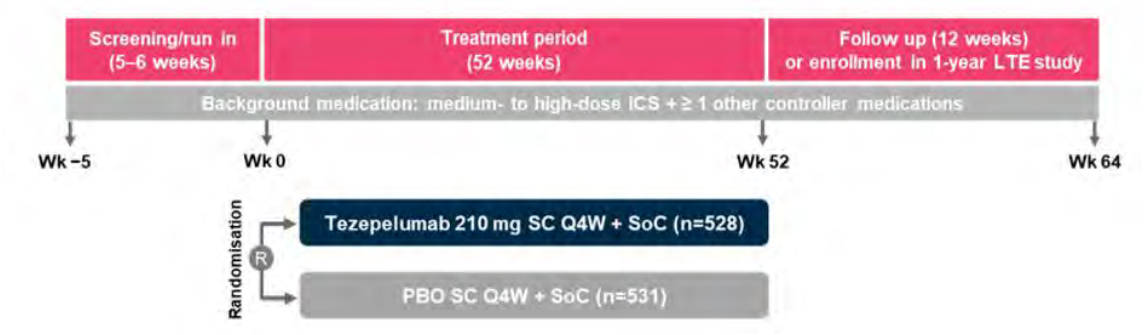
7.1 Efficacy and safety of tezepelumab compared to SoC for T2 high (SEA+ allergic) and T2 low

7.1.1 Relevant studies for tezepelumab vs SoC (high-dose ICS/LABA and +/- other controller medication)

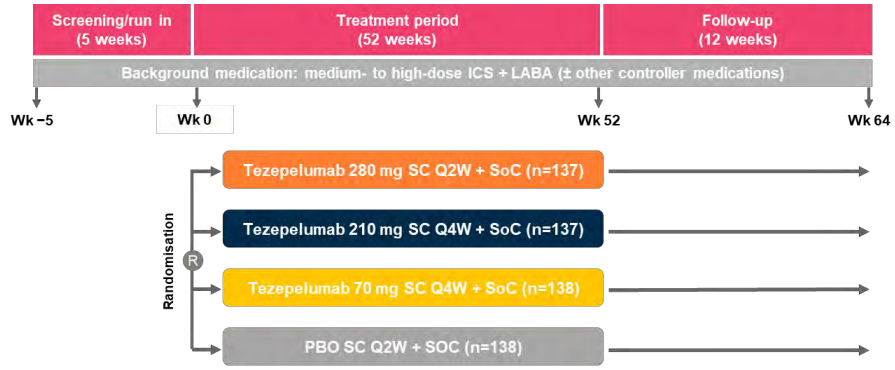
Tezepelumab has been studied in three pivotal studies, PATHWAY (Phase IIb), NAVIGATOR (Phase III) and SOURCE (Phase III) with the aim to evaluate the efficacy and safety of tezepelumab in adult patients with inadequately controlled, severe asthma. NAVIGATOR is the phase 3 study that included a broad range of patients with severe asthma independent of biomarker profile or OCS use. The other phase 3 study, SOURCE, only included 150 patients and an inclusion criteria was maintenance use of OCS. An overview of the NAVIGATOR, PATHWAY and SOURCE trial designs is presented in Figure 2.

Figure 3. Clinical trial designs for NAVIGATOR, PATHWAY and SOURCE

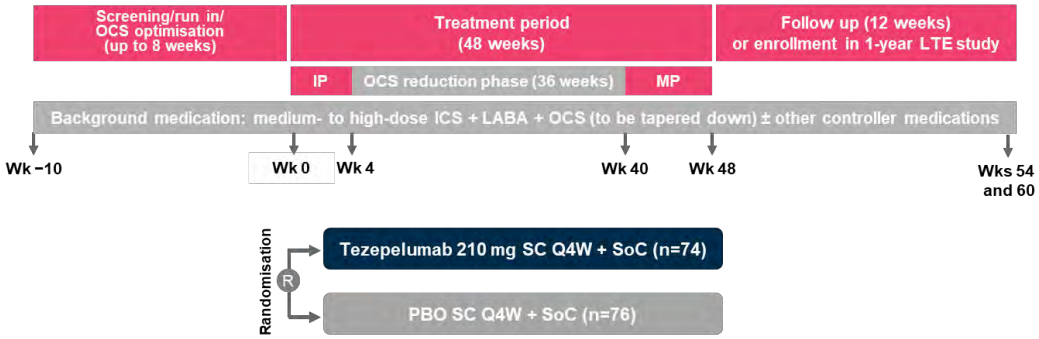
NAVIGATOR



PATHWAY



SOURCE



Abbreviations: *ICS inhaled corticosteroid; IP induction phase; LABA long-acting beta-agonist; LTE long-term extension; MP maintenance phase; OCS oral corticosteroid; PBO placebo; R, randomisation; Q2W every two weeks; Q4W every four weeks; SC subcutaneous; SoC standard of care; Wk Week.*

Sources: *Corren 2017;(1) Menzies-Gow 2021;(53) Wechsler 2022.(18)*

Table 9 shows key baseline demographic and clinical characteristics of study patients in NAVIGATOR and PATHWAY. Demographics were well-balanced between treatment groups in the trial and were representative of the target population. In NAVIGATOR, patients with a broad range of severe asthma phenotypes and baseline biomarker profiles were included, as indicated by the blood EOS and allergic status subgroups in Table 8. A wide spectrum of the blood EOS range was represented, allowing for robust subgroup analyses.

Table 9. The key baseline demographic and clinical characteristics of study patients in NAVIGATOR and PATHWAY

	NAVIGATOR		PATHWAY	
	PBO Q4W + SoC (n=531)	Teze 210 mg + SoC (n=528)	PBO Q4W + SoC (n=138)	Teze + SoC (n=137)
Age, years Mean (SD)	49.0 (15.9)	49.9 (16.3)	52.3 (11.7)	52.7 (12.7)
Sex Male, n (%)	194 (36.5)	193 (36.6)	44 (31.9)	50 (36.5)
OCS use Yes, n (%) No, n (%)	51 (9.6) 480 (90.4)	49 (9.3) 479 (90.7)	14 (10.1) 124 (89.9)	9 (6.6) 128 (93.4)
Exacerbations in past 12 months[a] 2,[b] n (%) ≥3, n (%)	325 (61.2) 206 (38.8)	310 (58.7) 218 (41.3)	110 (79.7) 28 (20.3)	105 (76.6) 32 (23.4)
Blood EOS, cells/µL <300, n (%) ≥300, n (%) <150, n (%) 150 to <300, n (%) 300 to <450, n (%) ≥450, n (%)	309 (58.2) 222 (41.8) 138 (26.0) 171 (32.2) 95 (17.9) 127 (23.9)	309 (58.5) 219 (41.5) 138 (26.1) 171 (32.4) 99 (18.8) 120 (22.7)	67 (48.6) 71 (51.4) - - - -	69 (50.4) 68 (49.6) - - - -
FeNO, ppb[c] Mean (SD)	46.3 (44.7)	41.4 (36.3)	37.8 (39.7)	31.5 (29.8)
Allergic status[d] Allergic Non-allergic Unknown	341 (64.2) 177 (33.3) 13 (2.4)	339 (64.2) 184 (34.8) 5 (0.9)	80 (61.5) 50 (38.5) -	77 (60.6) 50 (39.4) -

Footnotes: [a]An asthma exacerbation was defined as a worsening of asthma that either required treatment with a burst of SCS for at least three days or a single depot-injectable corticosteroid dose, or resulted in an ER visit which required SCS, or an inpatient hospitalisation due to asthma. For patients receiving a stable maintenance dose of OCS, a temporary increase for at least three consecutive days over and above the stable existing maintenance dose qualified as an exacerbation. [b]One patient in NAVIGATOR, enrolled in error, had one exacerbation in the year prior to the study and was included in the subgroup of subjects with two exacerbations in the year prior to the study. [c]High FeNO is indicative of type 2 inflammation. FeNO was recorded as the average of up to three measurements within 10% difference of each other. [d]In PATHWAY, allergic asthma was defined as a baseline positive IgE FEIA level to one or more region-specific allergens. In NAVIGATOR and SOURCE, allergic asthma was defined as a baseline positive perennial aeroallergen-specific IgE status (FEIA).

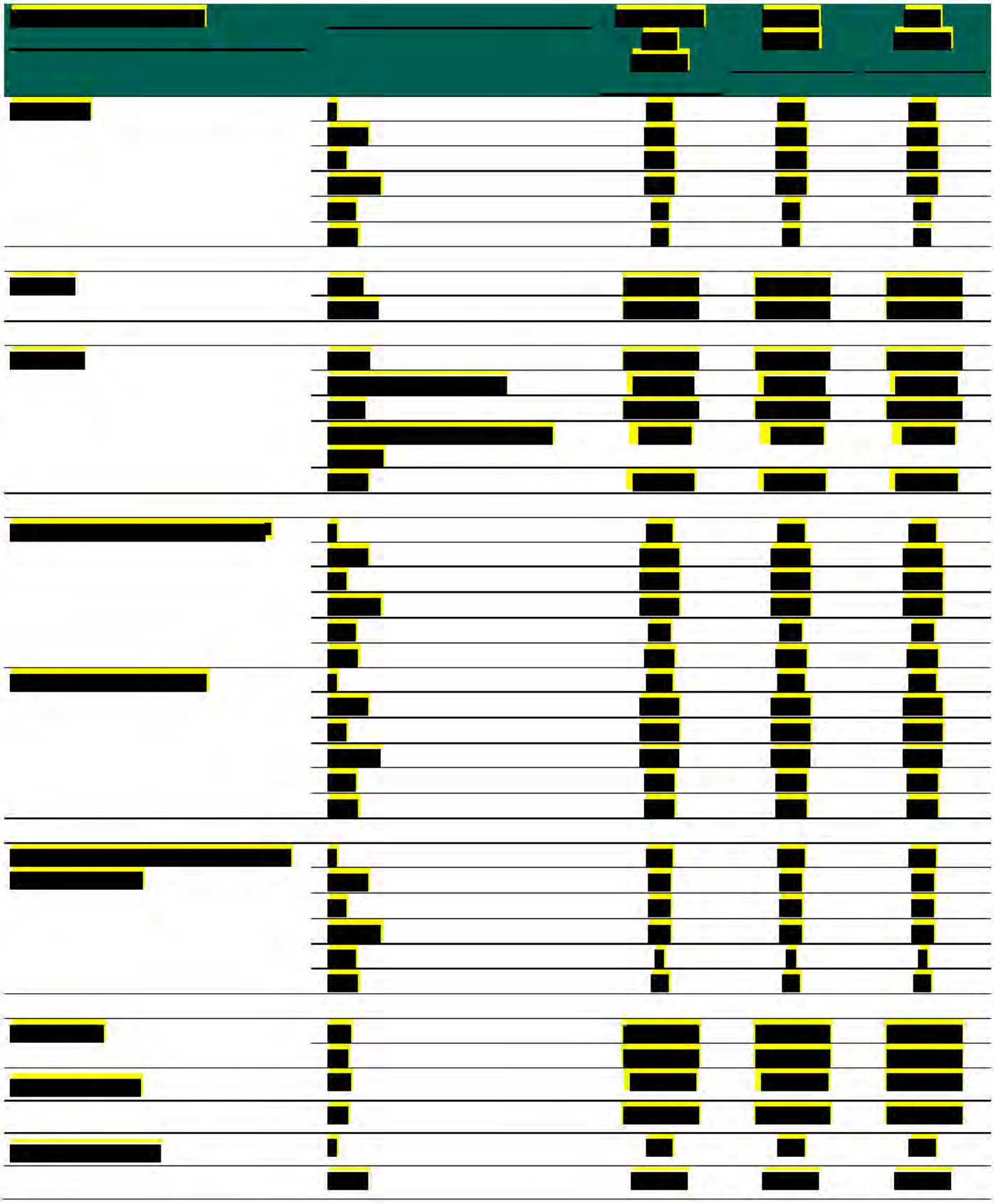
Abbreviations: EOS: eosinophil; ER: emergency room; FEIA: fluorescent enzyme immunoassay; FENO: fractional exhaled nitric oxide; IgE: immunoglobulin E; OCS: oral corticosteroid; PBO: placebo; SD: standard deviation; SoC: standard of care; teze: tezepelumab.

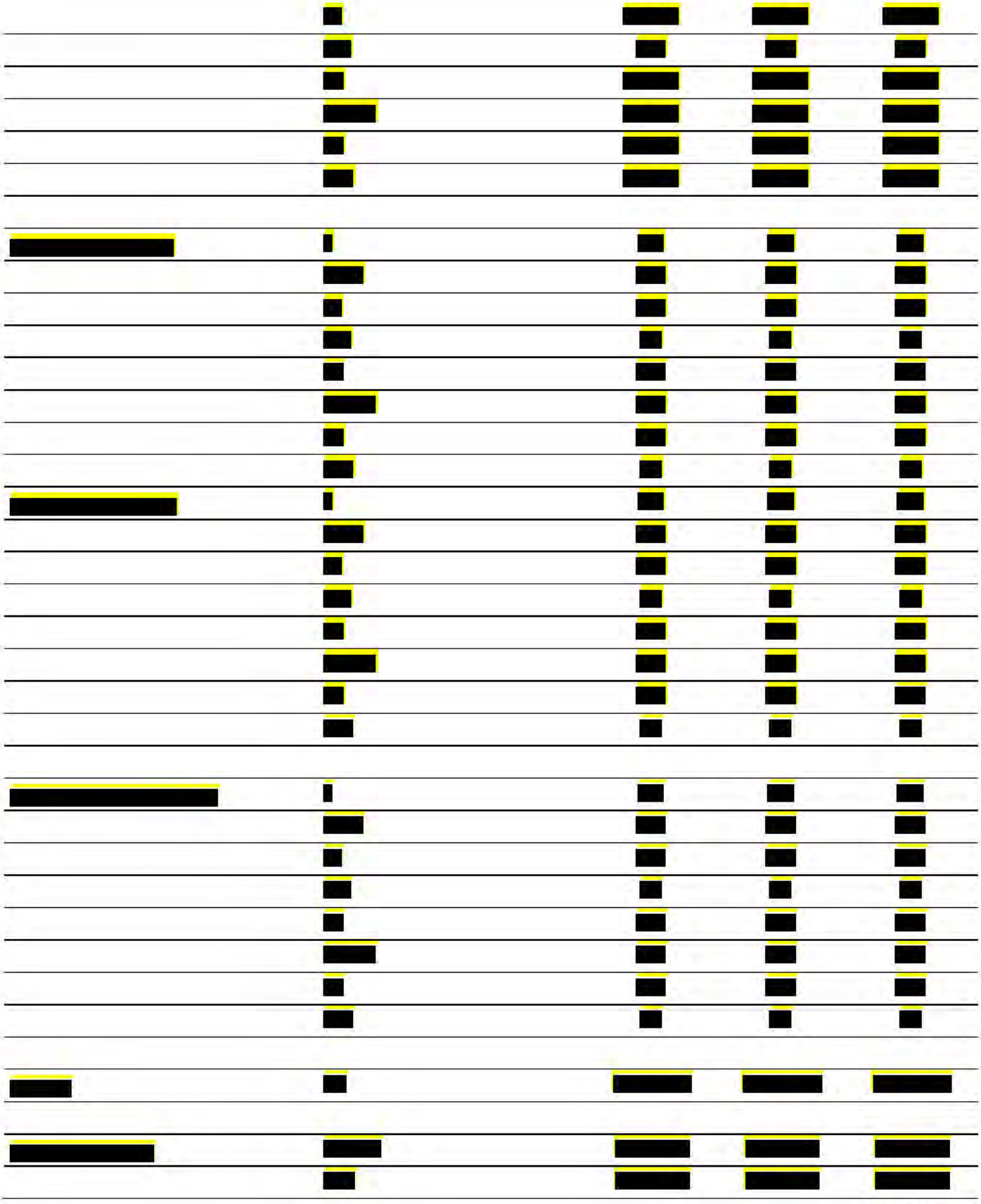
Sources: NAVIGATOR: Menzies-Gow 2021;(8) AstraZeneca/Amgen Data on File 2021;(20) PATHWAY: Corren 2017,(1) AstraZeneca/Amgen Data on File 2018;(17) SOURCE: Wechsler 2022.((18))

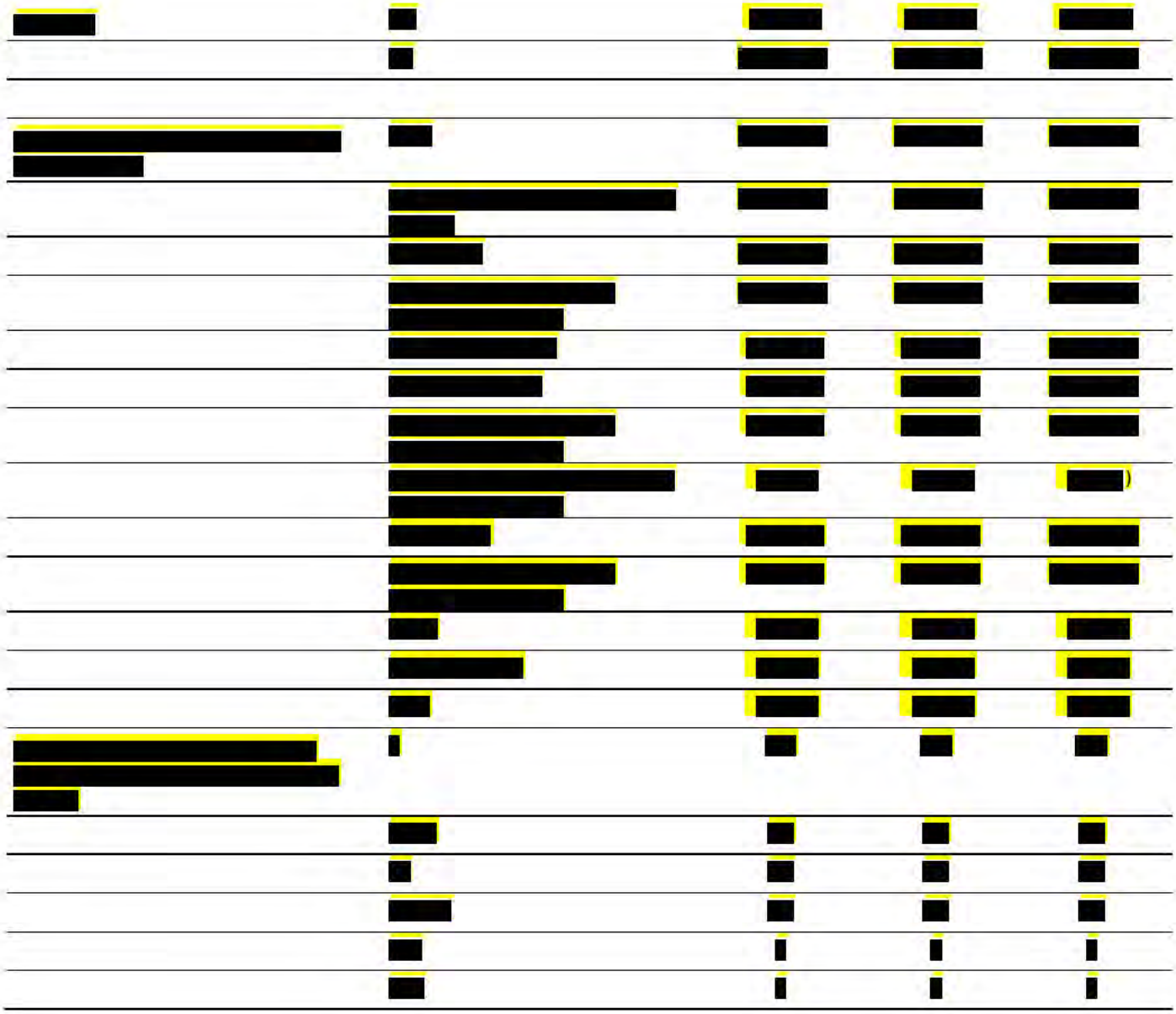
NAVIGATOR and PATHWAY are the studies including more patients with a borad range of phenotypes hence the data presented is focused on those studies.

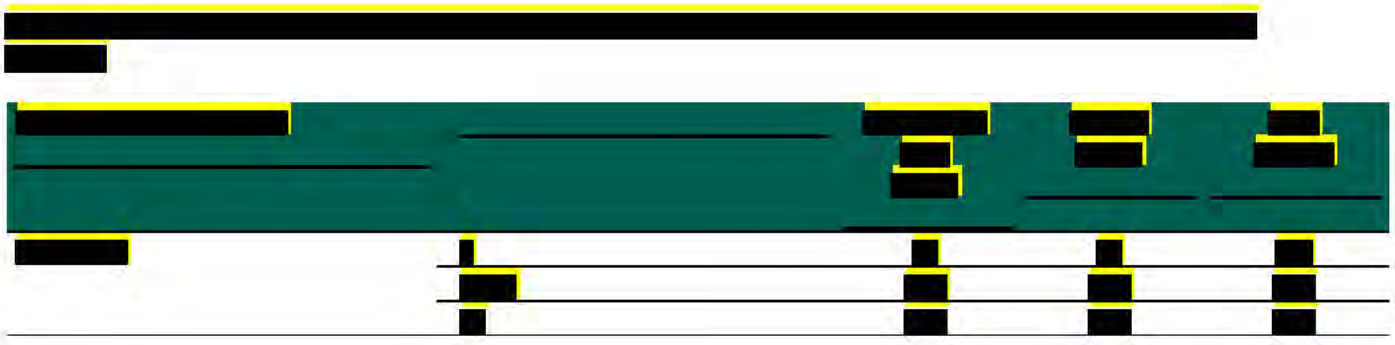
7.1.2 Efficacy and safety – results per study

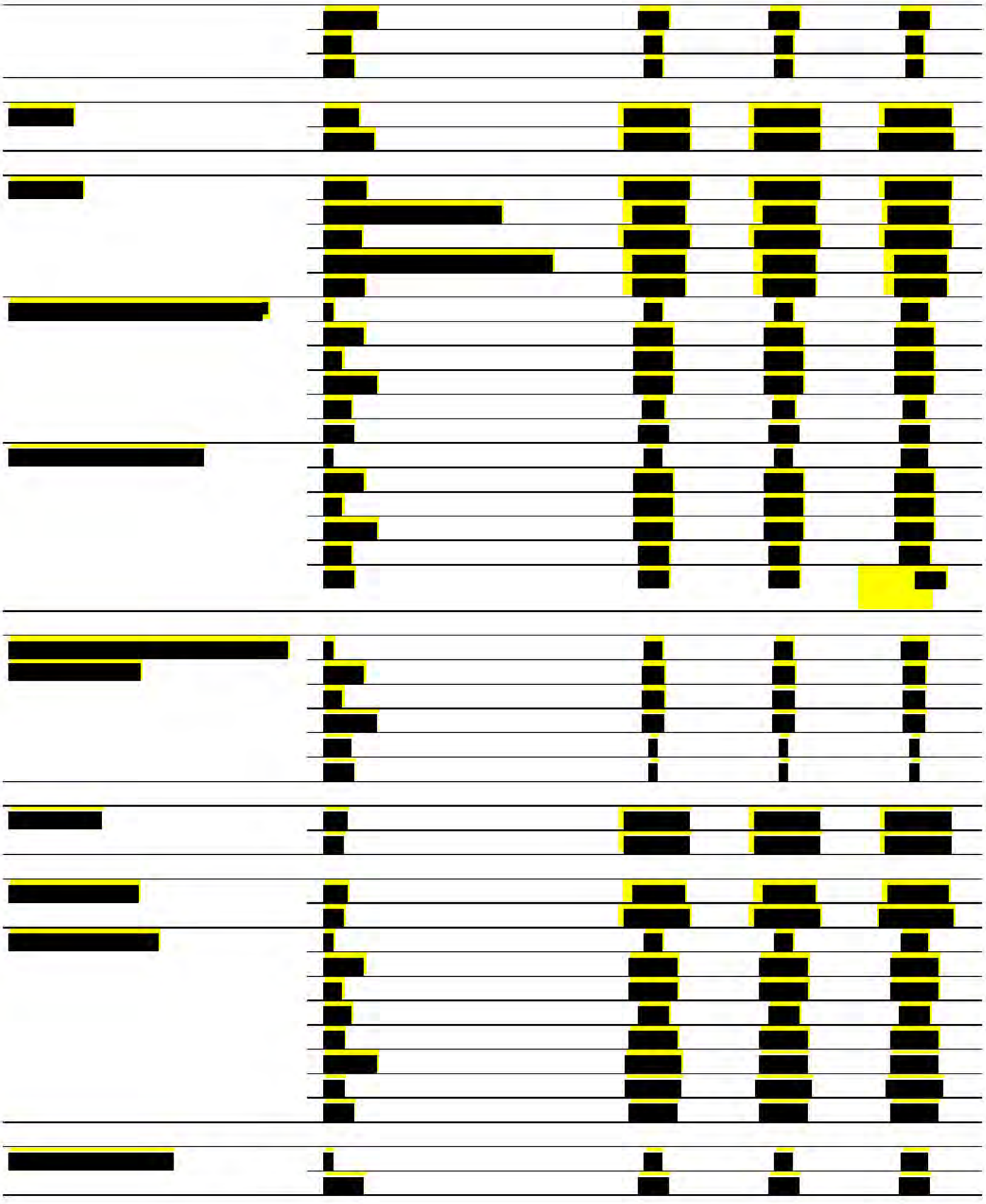
[redacted]

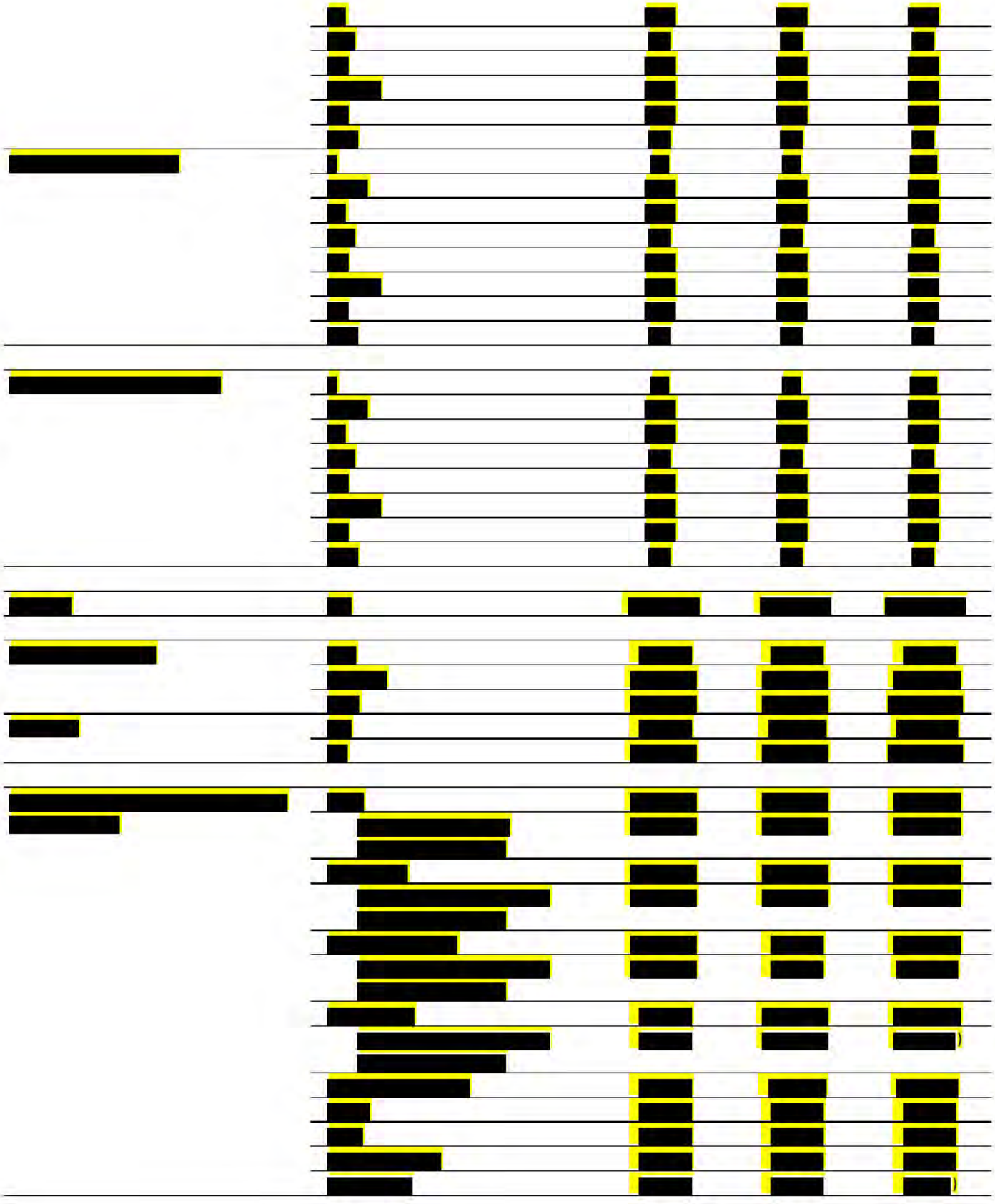


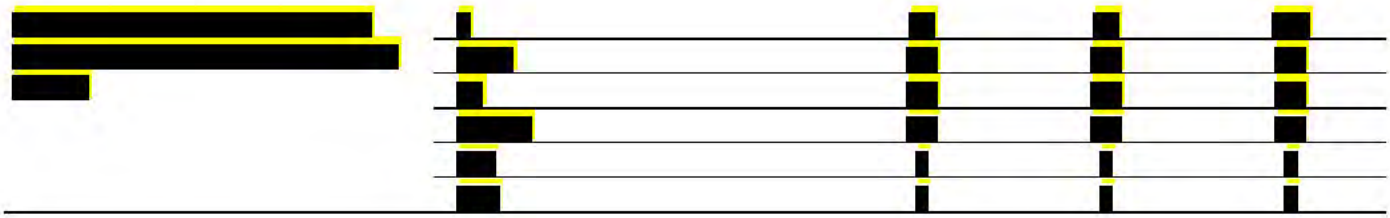








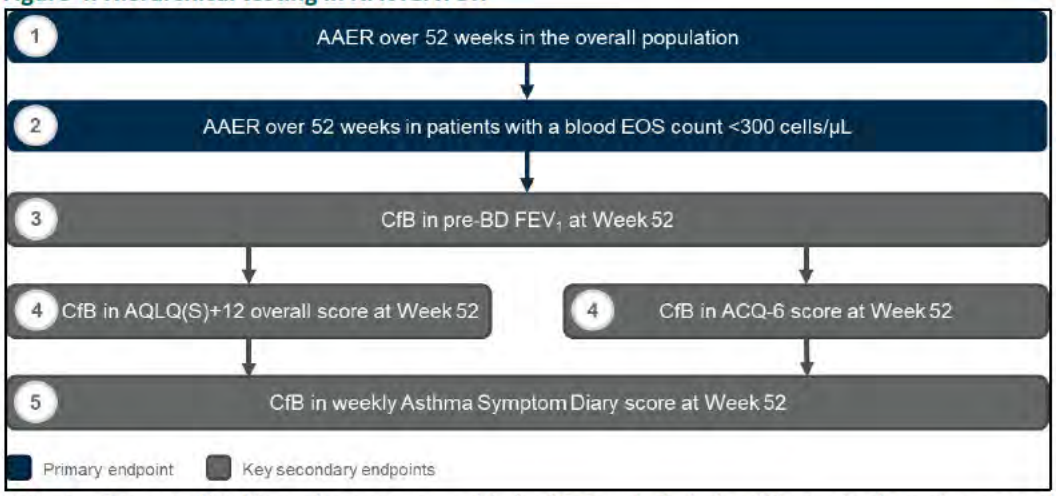




Multiple testing procedure in NAVIGATOR

A key strength of the NAVIGATOR trial was that all endpoints in the pre-specified hierarchical testing strategy, ordered by clinical relevance, met statistical significance. The subgroup of patients with baseline EOS <300 cells/µL was added to the multiple testing procedure at the request of the FDA, to support the Breakthrough Therapy Designation for tezepelumab for patients with severe asthma without an eosinophilic phenotype.(54, 55) This subgroup has a high unmet need due to the lack of available biologic treatment options, and the efficacy of tezepelumab in this subgroup is a key differentiator from other biologic treatments.

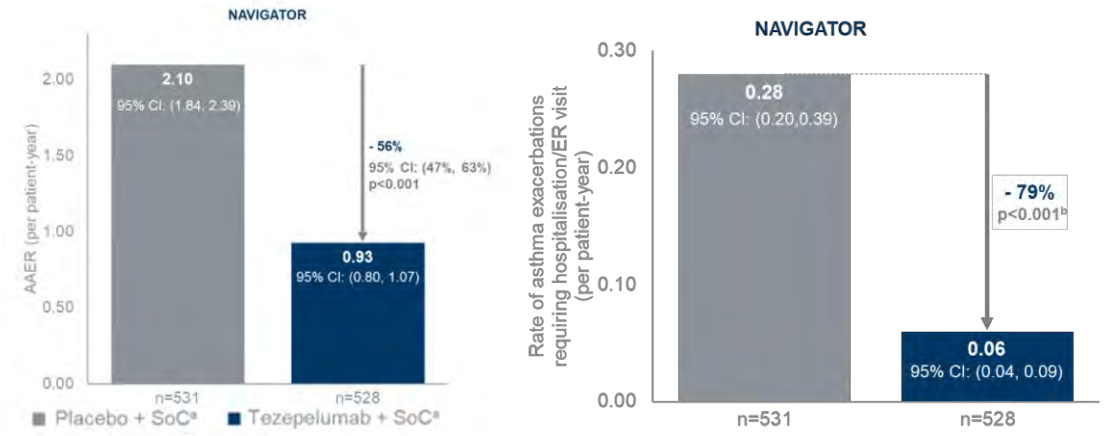
Figure 4. Hierarchical testing in NAVIGATOR



Footnotes: *A truncated Hochberg adjustment was used for level 4. As such, the higher of the two level 4 p values was evaluated at a 3.75% significance level (two-sided). As it was significant at the 3.75% level, both level 4 null hypotheses were rejected, and testing proceeded to level 5, which was tested at a two-sided 5% significance level.*

Sources: *Menzies-Gow 2020*

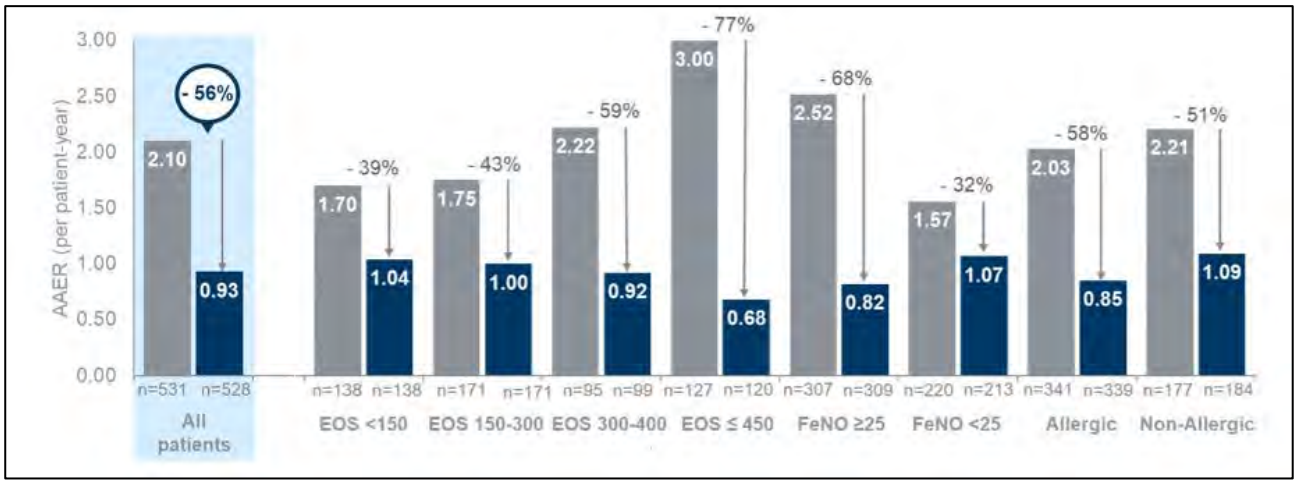
Figure 5. AAER at Week 52 to the left and reduction in exacerbations requiring hospitalisation or ER visit to the right (NAVIGATOR: FAS). Blue = tezepelumab + SoC and grey = Placebo + SoC.



***Source**: NAVIGATOR: Menzies-Gow 2021.*

- NAVIGATOR met its primary endpoints, as treatment with tezepelumab 210 mg Q4W + SoC resulted in statistically significant reductions in exacerbation rate of 56% (95% CI: 47%, 63%; nominal p<0.001) compared with the PBO Q4W + SoC group at Week 52 NAVIGATOR. (8)
- In NAVIGATOR, tezepelumab 210 mg Q4W + SoC treatment reduced the rate of asthma exacerbations requiring hospitalisation or ER visit compared with PBO Q4W + SoC over 52 weeks by 79% (AAER: 0.06 versus 0.28, respectively; RR: 0.21; 95% CI: 0.12, 0.37; nominal p<0.001) as shown in figure 4 (1, 7)
- Furthermore, the proportion of patients in NAVIGATOR who were followed for 52 weeks and did not experience asthma exacerbations requiring hospitalisation or ER visit was higher in the tezepelumab 210 mg Q4W + SoC group compared with the PBO Q4W + SoC group over 52 weeks (92.4% versus 85.1%, respectively; OR: 2.21; 95% CI: 1.47, 3.31).(20)
- The primary efficacy endpoint was assessed in a number of subgroups related to biomarker status and phenotype in the NAVIGATOR trial. Tezepelumab 210 mg Q4W + SoC demonstrated a consistent AAER reduction compared to PBO Q4W + SoC across phenotypes and irrespective of biomarker status over 52 weeks (see figure below for details). A statistically significant reduction in AAER was observed across EOS levels (nominal significance for all subgroups aside from EOS <300 cells/µL), with reductions ranging from 39% to 77% for EOS <150 cells/µL to ≥450 cells/µL, respectively, and allergic status (allergic: 58%; non-allergic: 51%).(8)

Figure 6 AAER by baseline biomarker status (NAVIGATOR; FAS)



***Source**: NAVIGATOR: Menzies-Gow 2021*

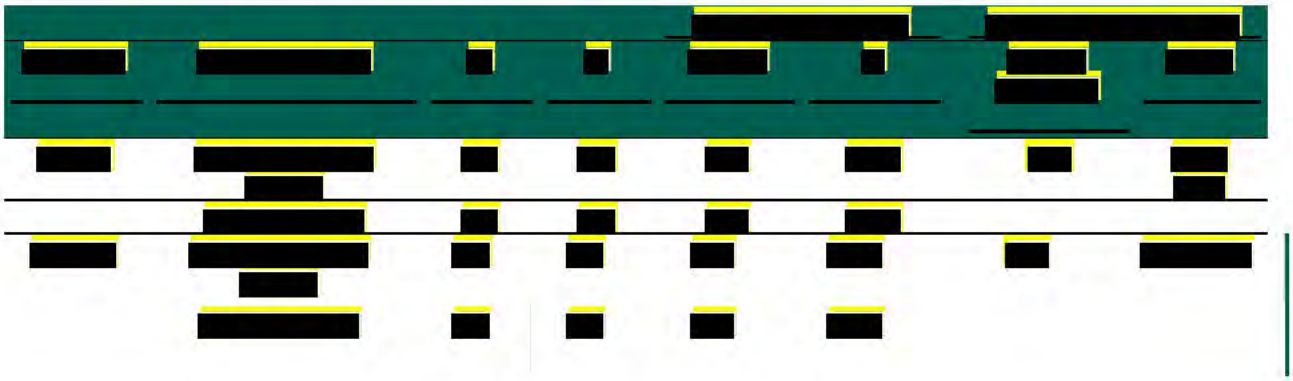
- Furthermore, pooled results across the PATHWAY and NAVIGATOR studies indicate a 60% reduction in exacerbation rate with tezepelumab 210 mg Q4W + SoC treatment compared with placebo Q4W + SoC (rate ratio [RR]: 0.40; 95% CI: 0.34, 0.48(56)

Below all results from NAVIGATOR are stated divided into the subpopulations requested by the Danish Medicines Council. First all the data for the T2 high population, defined as eosinophil counts ≥150/µL and/or FeNO ≥25 ppb, will be stated then the same results will be shared for the T2 low population defined as eosinophil counts <150/µL and FeNO <25 ppb. The same data have been included for PATHWAY, and some for SOURCE. In the end of this section more pooled data from NAVIGATOR and PATHWAY have been included.

Table 12 Annual asthma exacerbation rate ratio over 52 weeks, negative binomial model for participants with baseline eosinophil counts ≥150/µL and/or FeNO ≥25 ppb (NAVIGATOR)

Model: a negative binomial regression analysis with treatment, region, age group, history of exacerbations as covariates. The logarithm of the time at risk is used as an offset variable.
Annual exacerbation rates and absolute differences displayed are estimated marginal rates from the model. Absolute difference is the difference between the marginal rates.
Annual exacerbation rates displayed are estimated marginal rates from the model. Absolute difference is the difference between the marginal rates.
CIs for annual exacerbation rates and absolute differences are estimated via the delta method.
Teze = Tezepelumab. Q4W = every 4 weeks. N = Number of subjects in treatment group and given subgroup. n = Number of subjects in analysis. CI = Confidence interval.

Table 13 FEV1 (L) pre-bronchodilator change from baseline treatment comparison, mixed model for repeated measures analysis, for participants with baseline eosinophil counts ≥150/µL and/or FeNO ≥25 ppb



Baseline is defined as the last non-missing measurement recorded on or prior to randomisation.
Estimate of the mean change from baseline at each week in Tezepelumab is compared to the Placebo using a repeated measures analysis. Estimates are least squares means.
*The model with Unstructured covariance structure is: Change from baseline in FEV1 = Treatment group + region + age + baseline FEV1 + visit + treatment * visit.*
Subjects with data at baseline and at least at one post-baseline time point included in analysis.
Teze = Tezepelumab. Q4W = every 4 weeks. FEV1 = Forced expiratory volume in 1 second. FeNO = Fractional Exhaled Nitric Oxide. SE = Standard error. CI = Confidence interval. LS = Least Squares.
N = Number of subjects in treatment group. n1 = Number of subjects contributing to the analysis, i.e the number of subjects with at least one change from baseline value at any post baseline visit. n2 = Number of subjects with a change from baseline value at each timepoint

Table 14 ACQ-6 score change from baseline treatment comparison, mixed model for repeated measures analysis, for participants with baseline eosinophil counts ≥150/µL and/or FeNO ≥25 ppb

Baseline is defined as the last non-missing measurement recorded on or prior to randomisation.
The ACQ-6 score is computed as the unweighted mean of the responses to the 6 questoins. If response to any of the questions is missing, the ACQ-6 will be missing.
Estimate of the mean change from baseline at each week in Tezepelumab is compared to the Placebo using a repeated measures analysis. Estimates are least squares means.
*The model with Unstructured covariance structure is: Change from baseline in ACQ-6 = Treatment group + region + age + baseline ACQ-6 + visit + treatment * visit.*
Subjects with data at baseline and at least at one post-baseline time point included in analysis. Teze = Tezepelumab. Q4W = every 4 weeks. ACQ-6 = Asthma Control Questionnaire 6. FeNO = Fractional Exhaled Nitric Oxide. SE = Standard error. CI = Confidence interval. LS = Least Squares. N = Number of subjects in treatment group. n1 = Number of subjects contributing to the analysis, i.e the number of subjects with at least one change from baseline value at any post baseline visit. n2 = Number of subjects with a change from baseline value at each timepoint.

Table 15 AQLQ(S)+12 total score change from baseline treatment comparison, mixed model for repeated measures analysis, for participants with baseline eosinophil counts ≥150/µL and/or FeNO ≥25 ppb

Baseline is defined as the last non-missing measurement recorded on or prior to randomisation.
AQLQ(S)+12 Total score defined as the unweighted mean of the responses to all questions in the questionnaire. If response to any of the questions is missing, the Total score will be missing.
Estimate of the mean change from baseline at each week in Tezepelumab is compared to the Placebo using a repeated measures analysis. Estimates are least squares means.
*The model with Unstructured covariance structure is: Change from baseline in AQLQ(S)+12 = Treatment group + region + age + baseline AQLQ(S)+12 + visit + treatment * visit.*
Subjects with data at baseline and at least at one post-baseline time point included in analysis.
Teze = Tezepelumab. Q4W = every 4 weeks. AQLQ(S)+12 = Standardised Asthma Quality of Life Questionnaire for 12 Years and Older. FeNO =

Fractional Exhaled Nitric Oxide. SE = Standard error. CI = Confidence interval. LS = Least Squares. N = Number of subjects in treatment group. n1 = Number of subjects contributing to the analysis, i.e the number of subjects with at least one change from baseline value at any post baseline visit. n2 = Number of subjects with a change from baseline value at each timepoint.

Table 16 Annual asthma exacerbation rate ratio over 52 weeks, negative binomial model, for participants with baseline eosinophil counts <150/µL and FeNO <25 ppb

Table 17 FEV1 (L) pre-bronchodilator change from baseline treatment comparison, mixed model for repeated measures analysis, for participants with baseline eosinophil counts <150/µL and FeNO <25 ppb

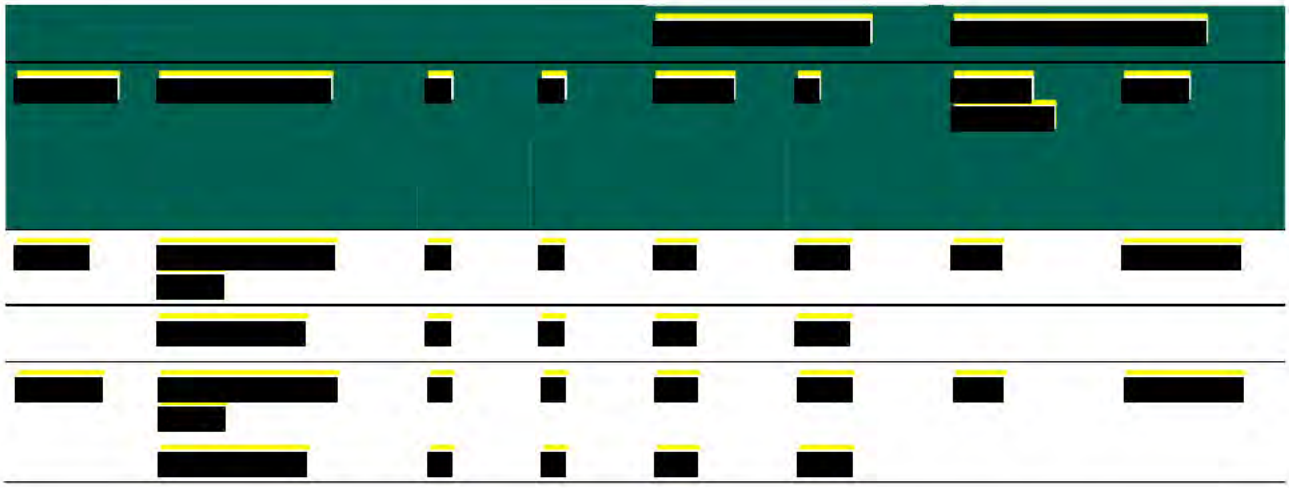


Table 18 ACQ-6 score change from baseline treatment comparison, mixed model for repeated measures analysis, for participants with baseline eosinophil counts <150/µL and FeNO <25 ppb

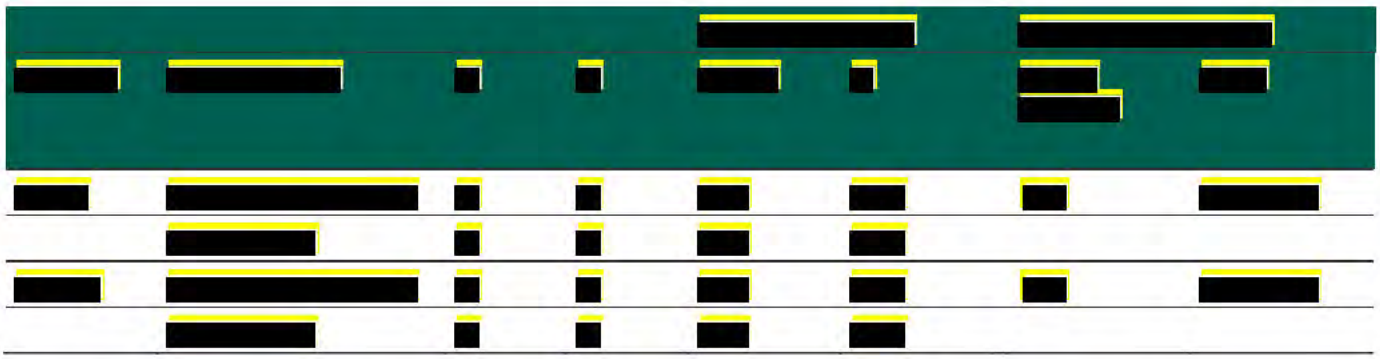


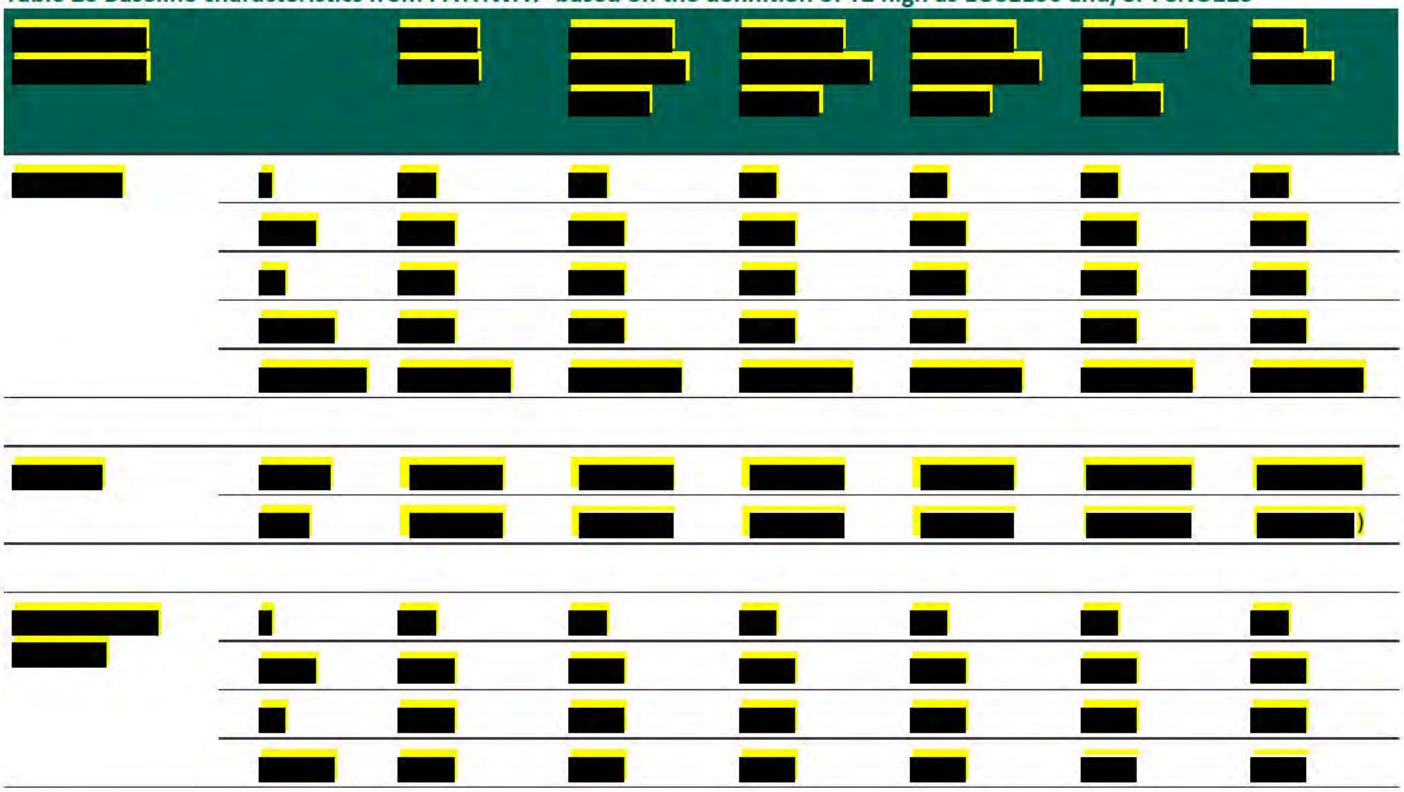
Table 19 AQLQ(S)+12 total score change from baseline treatment comparison, mixed model for repeated measures analysis, for participants with baseline eosinophil counts <150/µL and FeNO <25 ppb

- In NAVIGATOR, the proportion of patients who experienced no asthma exacerbations was higher in the tezepelumab 210 mg Q4W + SoC group (56.3%) compared with the PBO Q4W + SoC group (39.9%) in the overall population over 52 weeks.(8)
- In NAVIGATOR, patients receiving tezepelumab + SoC demonstrated a statistically significant and clinically meaningful improvement from baseline in pre-BD FEV1 compared with PBO + SoC (0.23 L versus 0.09 L, Least squares (LS) mean difference: 0.13 L; 95% CI: 0.08, 0.18; p<0.001).(7, 8)
- An FEV_1 change of at least 0.1 to 0.2 L was considered clinically meaningful.(57)
- ACQ-6 is a questionnaire to measure the adequacy of asthma control, and to capture changes in asthma control which occur either spontaneously or as a result of treatment. A lower score indicates better asthma control; therefore, a reduction in ACQ-6 score from baseline represents an improvement in asthma control. In the NAVIGATOR trial, a clinically meaningful improvement in ACQ-6 was defined as an improvement of 0.5 units.((58)) In NAVIGATOR, 86.2% of patients treated with tezepelumab + SoC experienced a clinically meaningful improvement in ACQ-6 score. Overall, a statistically significant mean improvement from baseline in ACQ-6 score was observed with tezepelumab + SoC treatment versus PBO + SoC.

- The AQLQ(S)+12 is a standardized measure of QoL and functional impairment in patients with asthma. An increase in the AQLQ(S)+12 score from baseline indicates an improvement in patient HRQoL, with a clinically meaningful improvement defined as a change of at least 0.5 units in the three trials.(59)
- In NAVIGATOR, a greater proportion of patients receiving tezepelumab + SoC treatment (77.5%) achieved clinically meaningful improvements in the AQLQ(S)+12 score compared with PBO + SoC (71.7%) (OR: 1.36; 95% CI: 1.02, 1.82).
- The SGRQ measures the health status in patients with diseases of airways obstruction. A total score was calculated from three domains: symptoms (frequency and severity), activities (that cause or are limited by breathlessness) and impacts (social functioning and psychological disturbances resulting from airways disease). Scores range from 0 to 100, with higher scores indicating more limitations. SGRQ was measured in the NAVIGATOR trial as an exploratory outcome, in which a minimum change in score of four units was considered clinically relevant.(60) In NAVIGATOR, more patients treated with tezepelumab + SoC achieved clinically meaningful improvements in SGRQ score compared with patients treated with PBO + SoC (OR: 1.66; 95% CI: 1.17, 2.36). A clinically meaningful and nominally significant difference in total SGRQ score was observed with tezepelumab + SoC compared with PBO + SoC (tezepelumab + SoC versus PBO + SoC LS mean change from baseline: -21.91 and -15.86; difference: -6.05; 95% CI -8.74, -3.37; nominal p<0.001 (21).
- In NAVIGATOR, treatment with tezepelumab + SoC resulted in clinically meaningful improvements from baseline and a statistically significant improvement compared with PBO + SoC in weekly mean total ASD scores (tezepelumab + SoC versus PBO + SoC LS mean change from baseline: -0.71 versus -0.59; difference: -0.12; p=0.002).

Efficacy results from PATHWAY

Table 20 Baseline characteristics from PATHWAY based on the definition of T2 high as EOS≥150 and/or FeNO≥25



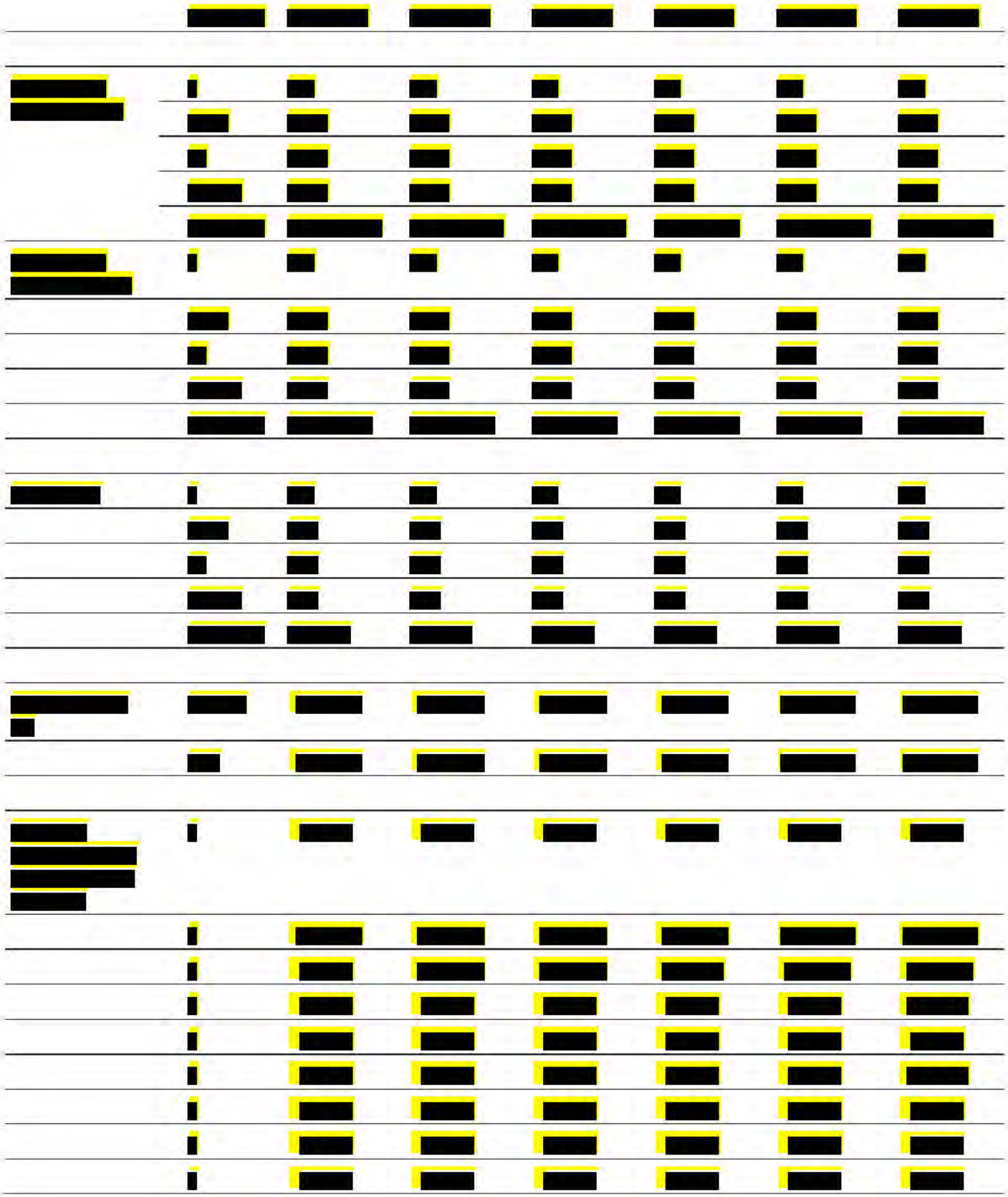
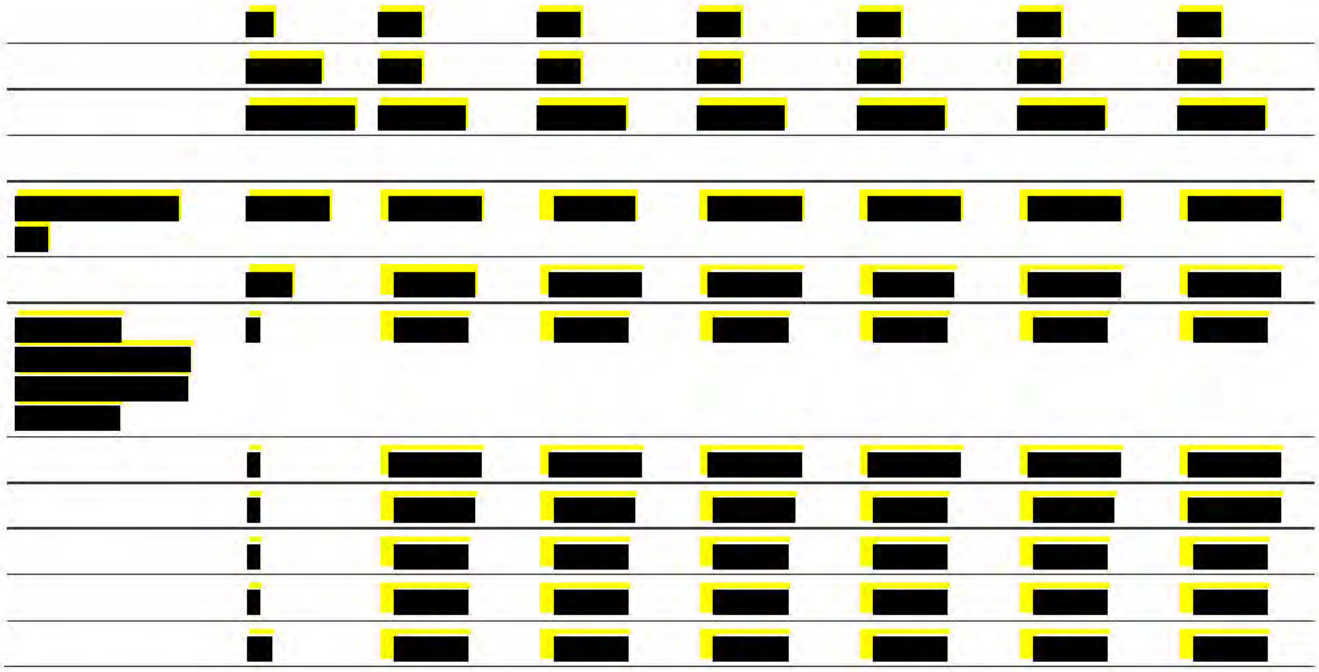


Table 21 Baseline characteristics from PATHWAY based on the definition of T2 low as EOS<150 and FeNO<25



This section only presents baseline characteristics and clinical efficacy results for patients treated with tezepelumab 210 mg Q4W + SoC and PBO Q4W + SoC as this is the dose of the indication and the dose used in pooled analyses which was shown above in the NAVIGATOR section.

- PATHWAY met its primary endpoints, as treatment with tezepelumab 210 mg Q4W + SoC resulted in statistically significant reductions in exacerbation rate of 71% (90% CI: 54%, 82%; p<0.001) compared with the PBO Q4W + SoC group at Week 52 as shown in Figure 7.(1)

- In PATHWAY, tezepelumab 210 mg Q4W + SoC treatment reduced the rate of asthma exacerbations requiring hospitalisation or ER visit compared with PBO Q4W + SoC over 52 weeks by 85% (AAER: 0.03 versus 0.18, respectively; RR: 0.15; 95% CI: 0.04, 0.58; nominal p=0.005 as shown in Figure 7.(1)

- Furthermore, PATHWAY results indicated that, among patients admitted to the hospital or the ICU, those treated with tezepelumab 210 mg Q4W + SoC (n=8/137) reported fewer mean days in the hospital compared with PBO Q2W + SoC (n=16/138) over 52 weeks (6 versus 23 days, respectively; RR: 0.15; 95% CI: 0.03, 0.89) and fewer mean days in the ICU (RR: 0.001; 95% CI: 0.00, 0.45).(61)

- In PATHWAY, 84.7% of patients treated with tezepelumab 210 mg Q4W + SoC had zero asthma exacerbations through Week 52, compared with 68.8% in the PBO Q2W + SoC group.(17)

- In PATHWAY 81.8% of patients treated with tezepelumab + SoC experienced a clinically meaningful improvement in ACQ-6 score.(1)

Table 22 Annual asthma exacerbation rate ratio over 52 weeks, negative binomial model, for participants with baseline eosinophil counts ≥150/µL and/or FeNO ≥25 ppb

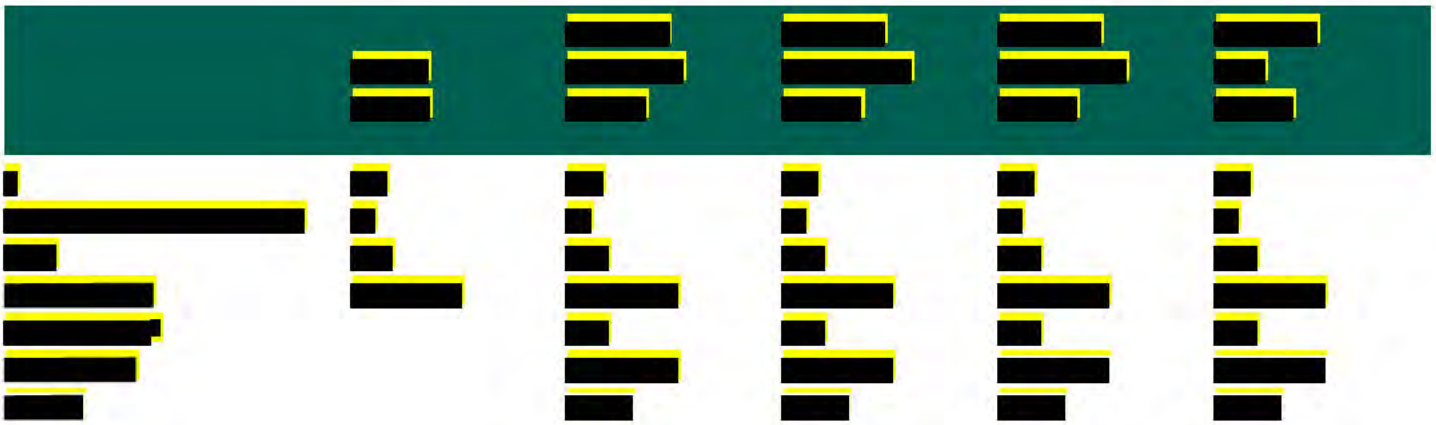


Table 23 Summary of change from baseline in FEV1 for participants with baseline eosinophil counts ≥150/µL and/or FeNO ≥25 ppb

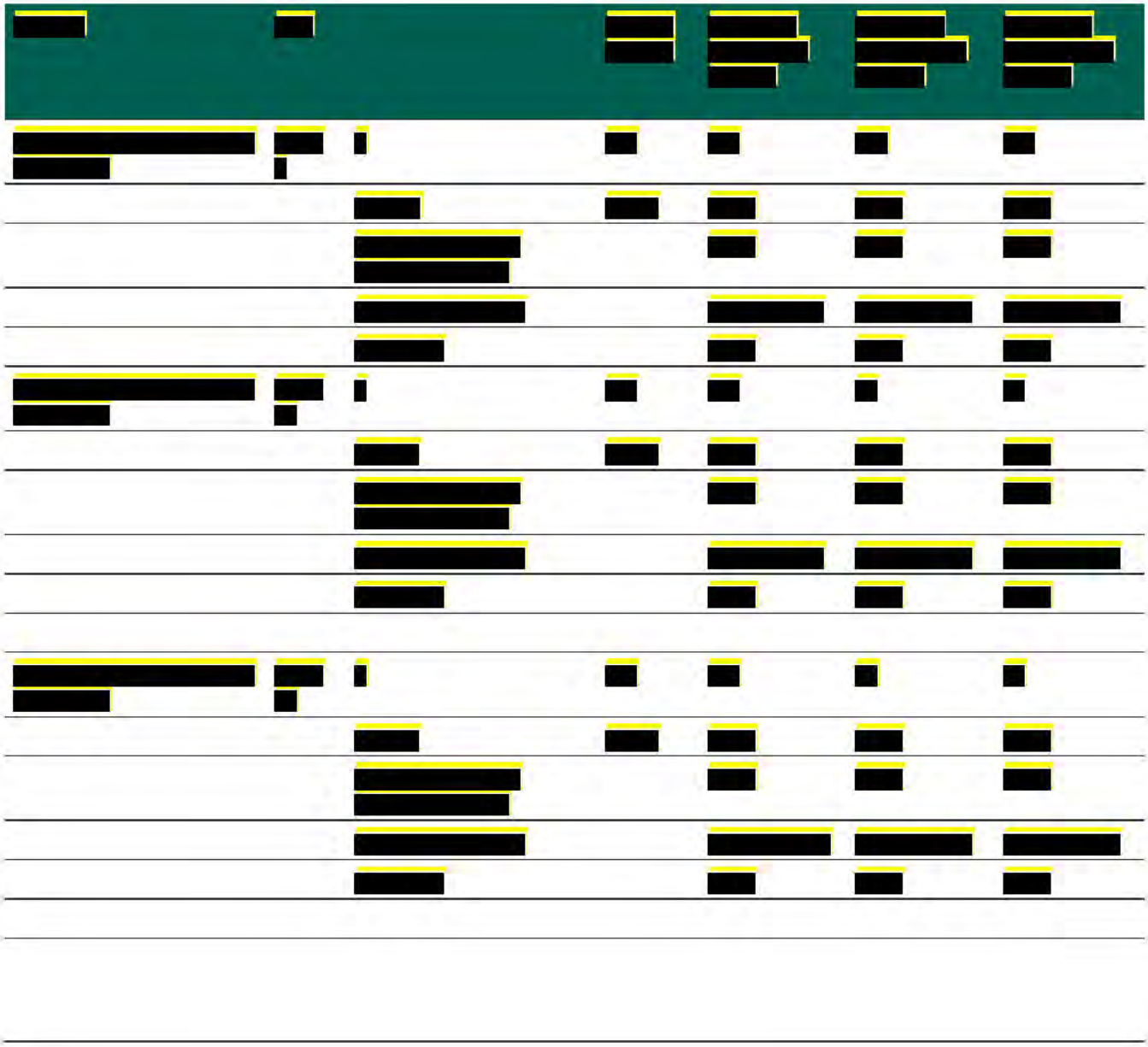


Table 24 Summary of change from baseline in mean ACQ-6 score, for participants with baseline eosinophil counts ≥150/µL and/or FeNO ≥25 ppb

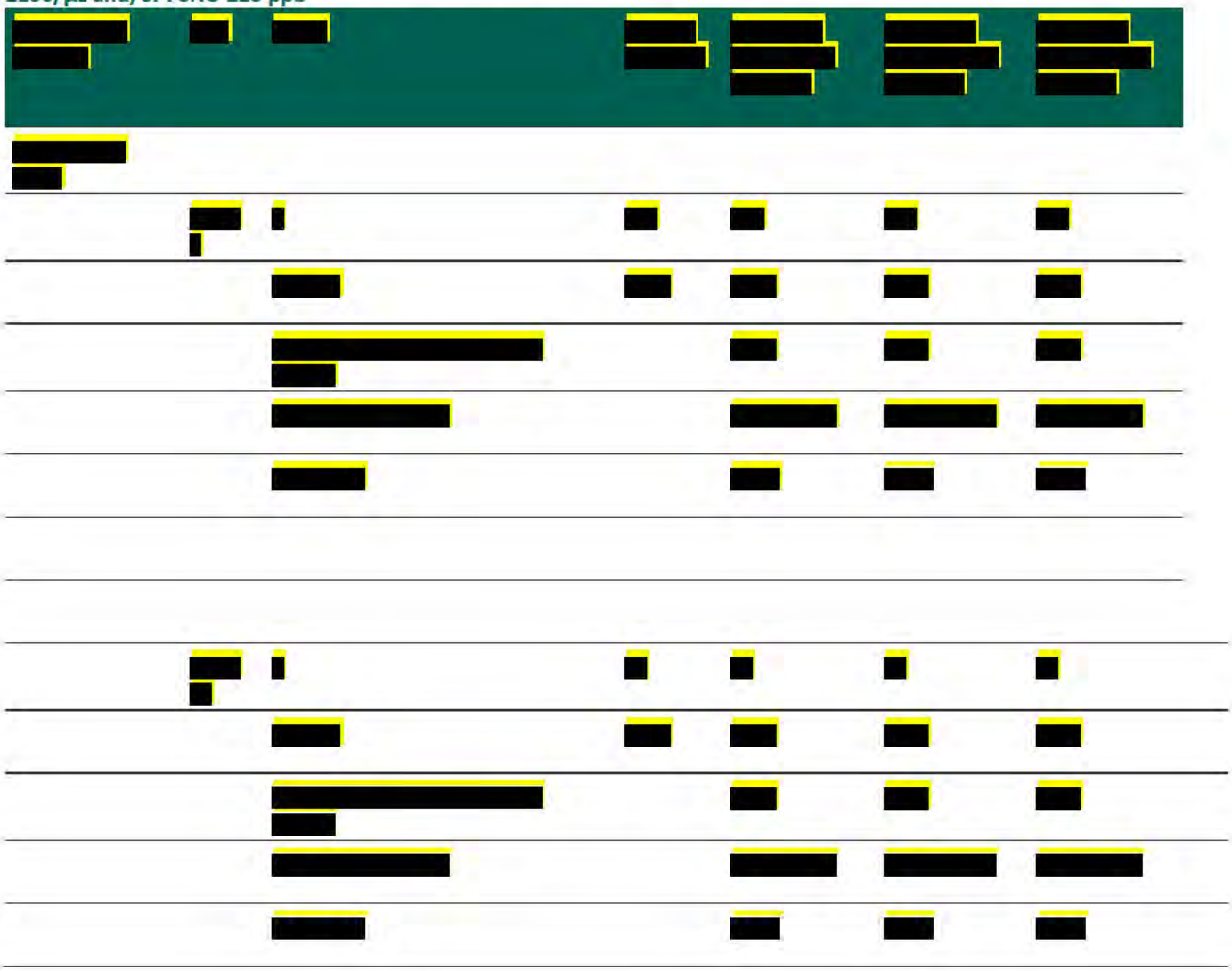


Table 25 Summary of change from baseline in AQLQ(S)+12 overall score for participants with baseline eosinophil counts ≥150/µL and/or FeNO ≥25 ppb

Table 26 Annual asthma exacerbation rate ratio over 52 weeks, negative binomial model, for participants with baseline eosinophil counts <150/µL and FeNO <25 ppb

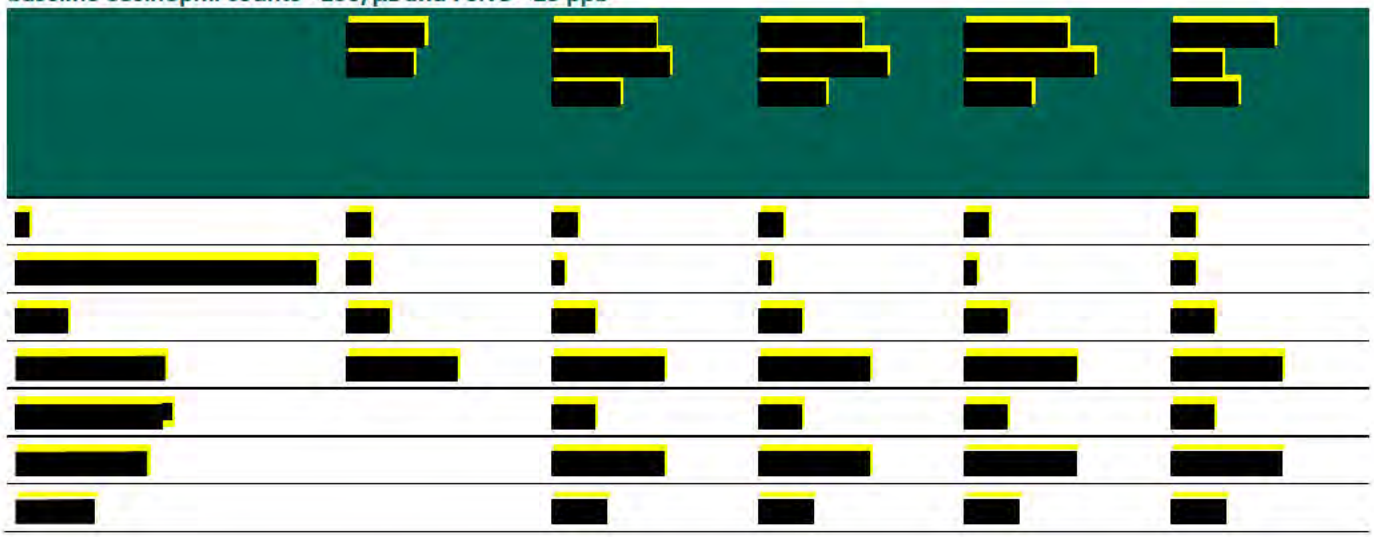
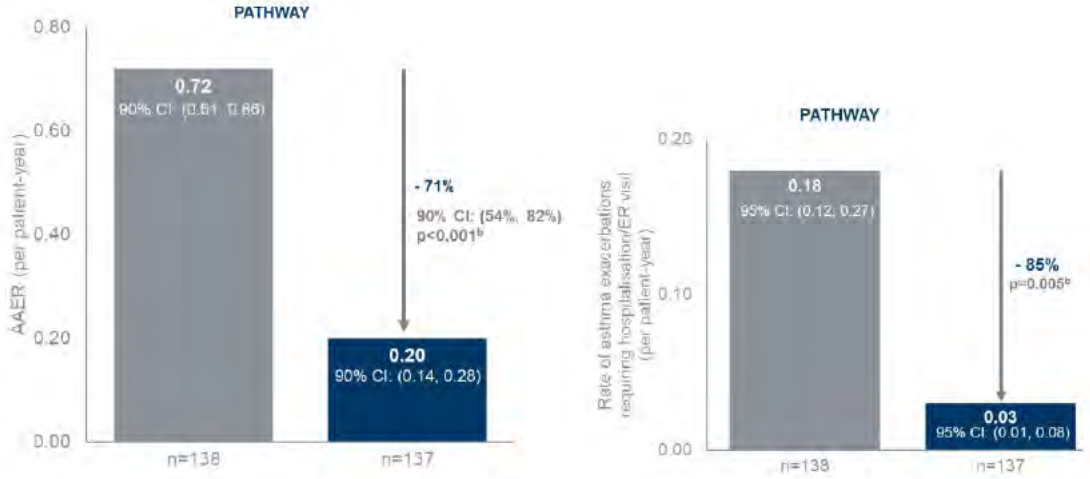


Table 27 Summary of change from baseline in FEV1, for participants with baseline eosinophil counts <150/µL and FeNO <25 ppb

Table 28 Summary of change from baseline in mean ACQ-6 score, for participants with baseline eosinophil counts <150/µL and FeNO <25 ppb

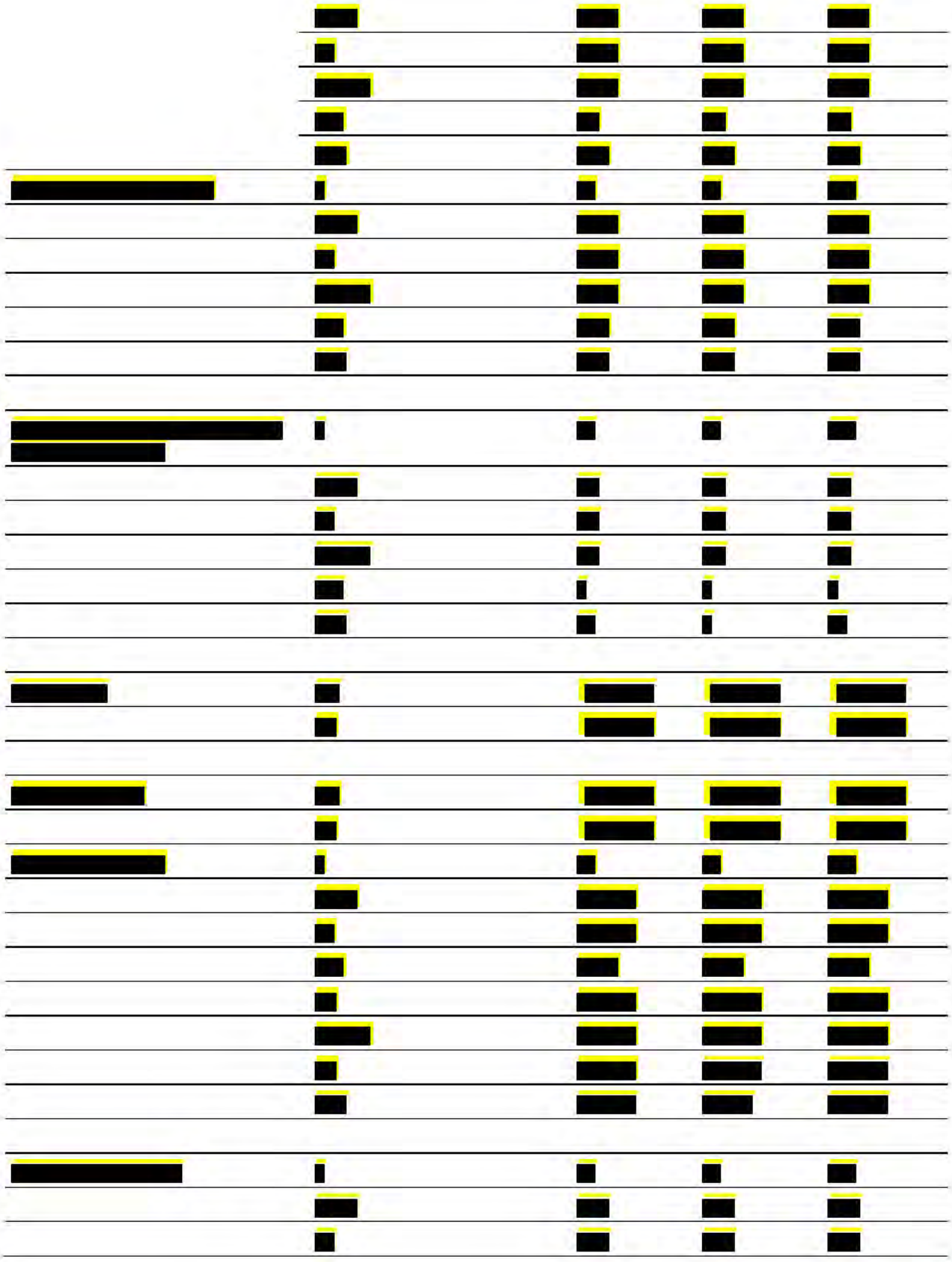
Table 29 Summary of change from baseline in AQLQ(S)+12 overall score, for participants with baseline eosinophil counts <150/µL and FeNO <25 ppb

Figure 7. AAER at Week 52 to the left and reduction in exacerbations requiring hospitalisation or ER visit to the right (PATHWAY: ITT). Blue = tezepelumab + SoC and grey = Placebo + SoC.



Efficacy results from SOURCE

Table 30 Baseline characteristics from SOURCE based on a T2 high population defined as baseline eosinophil counts ≥150/µL and/or FeNO ≥25 ppb



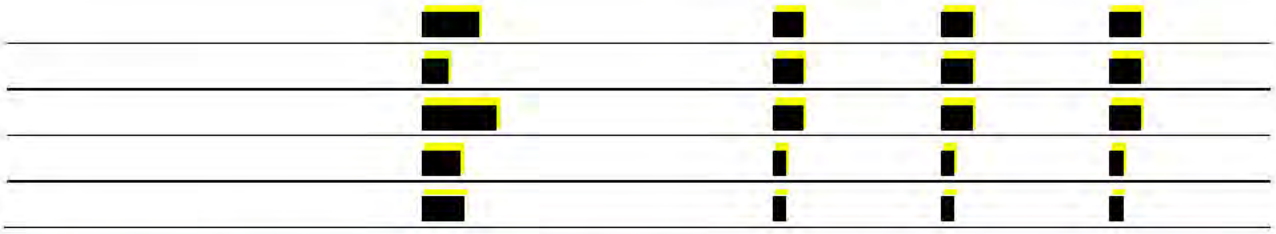
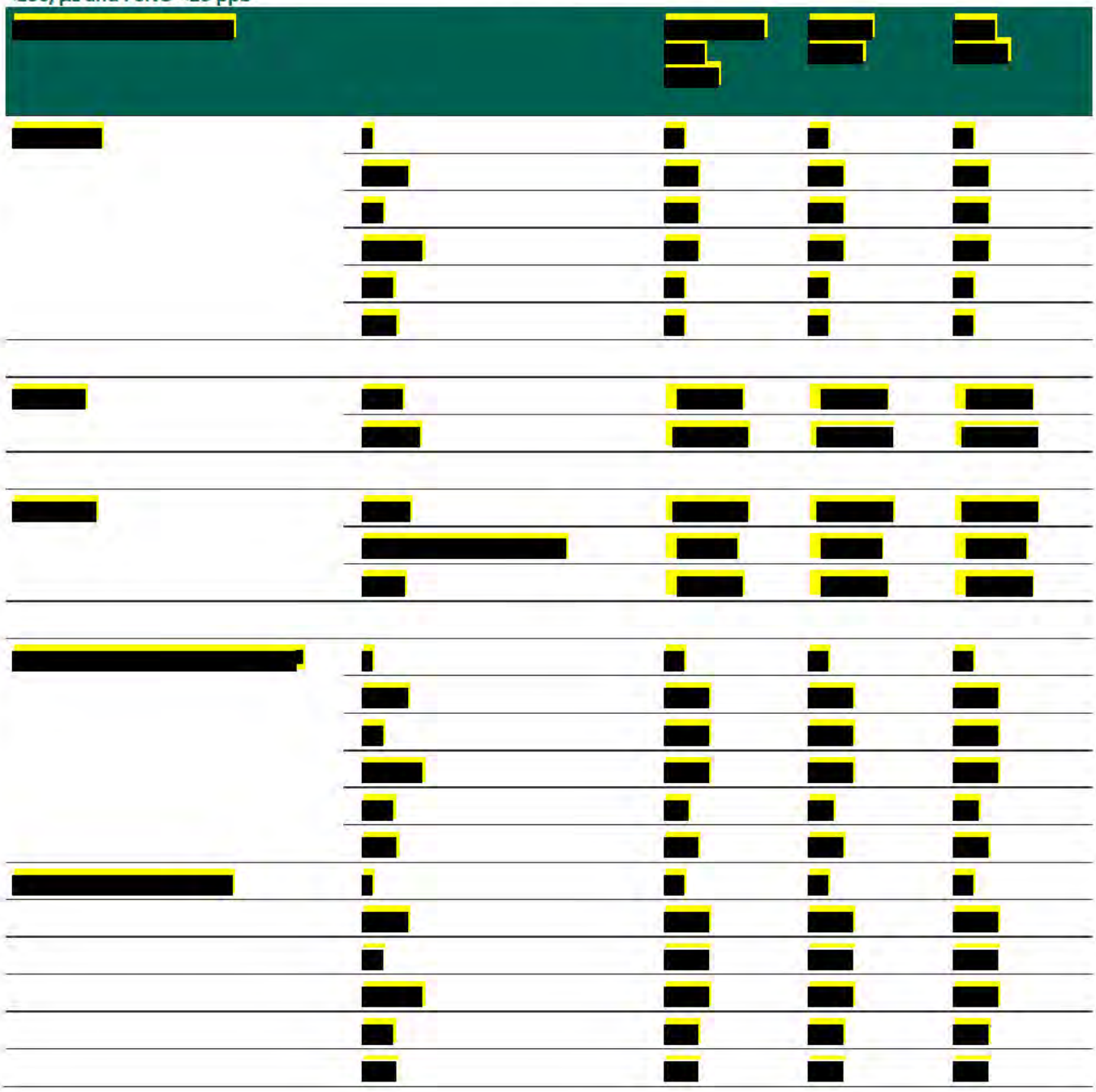
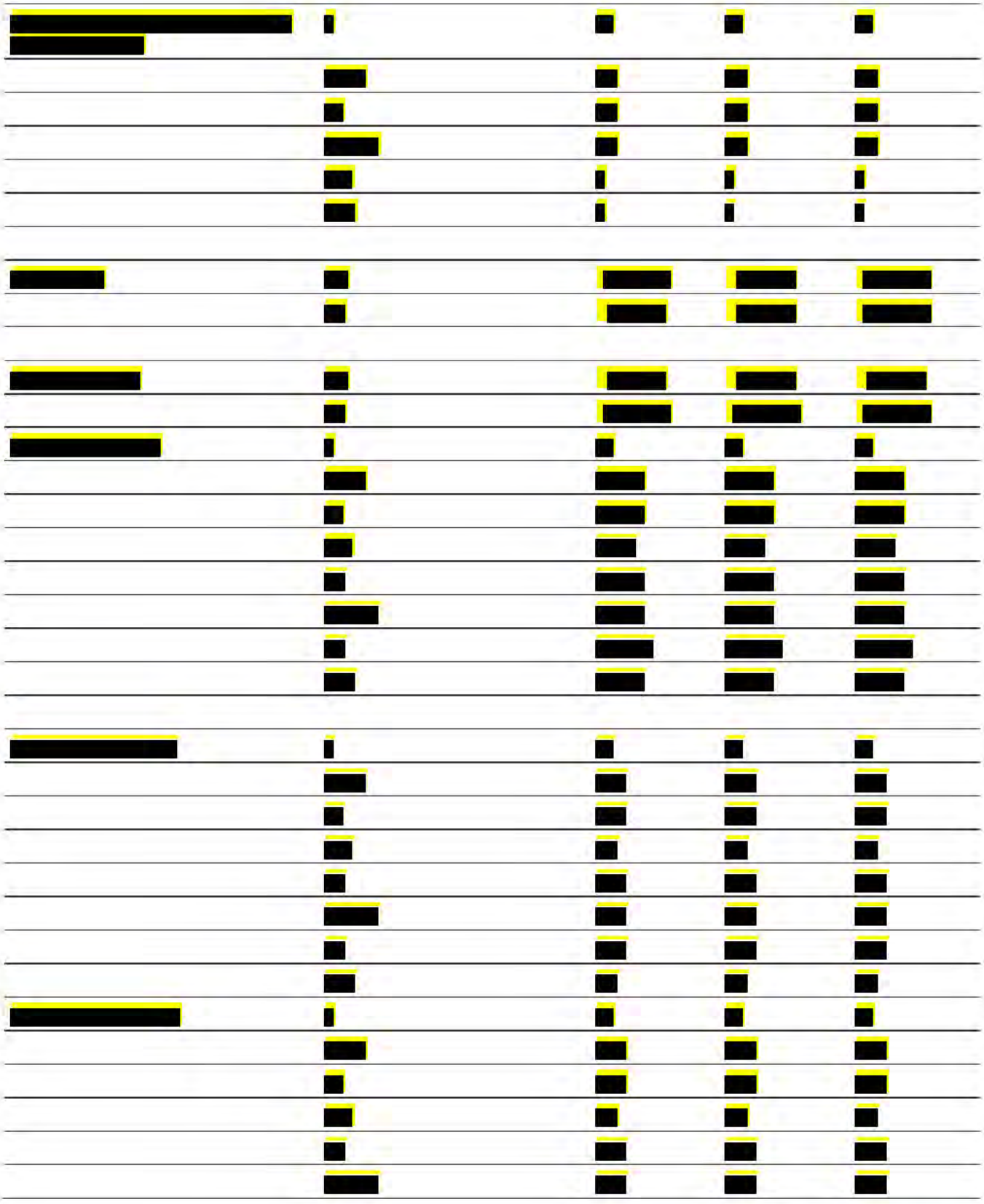


Table 31 Baseline characteristics from SOURCE based on a T2 low population defined as baseline eosinophil counts <150/µL and FeNO <25 ppb





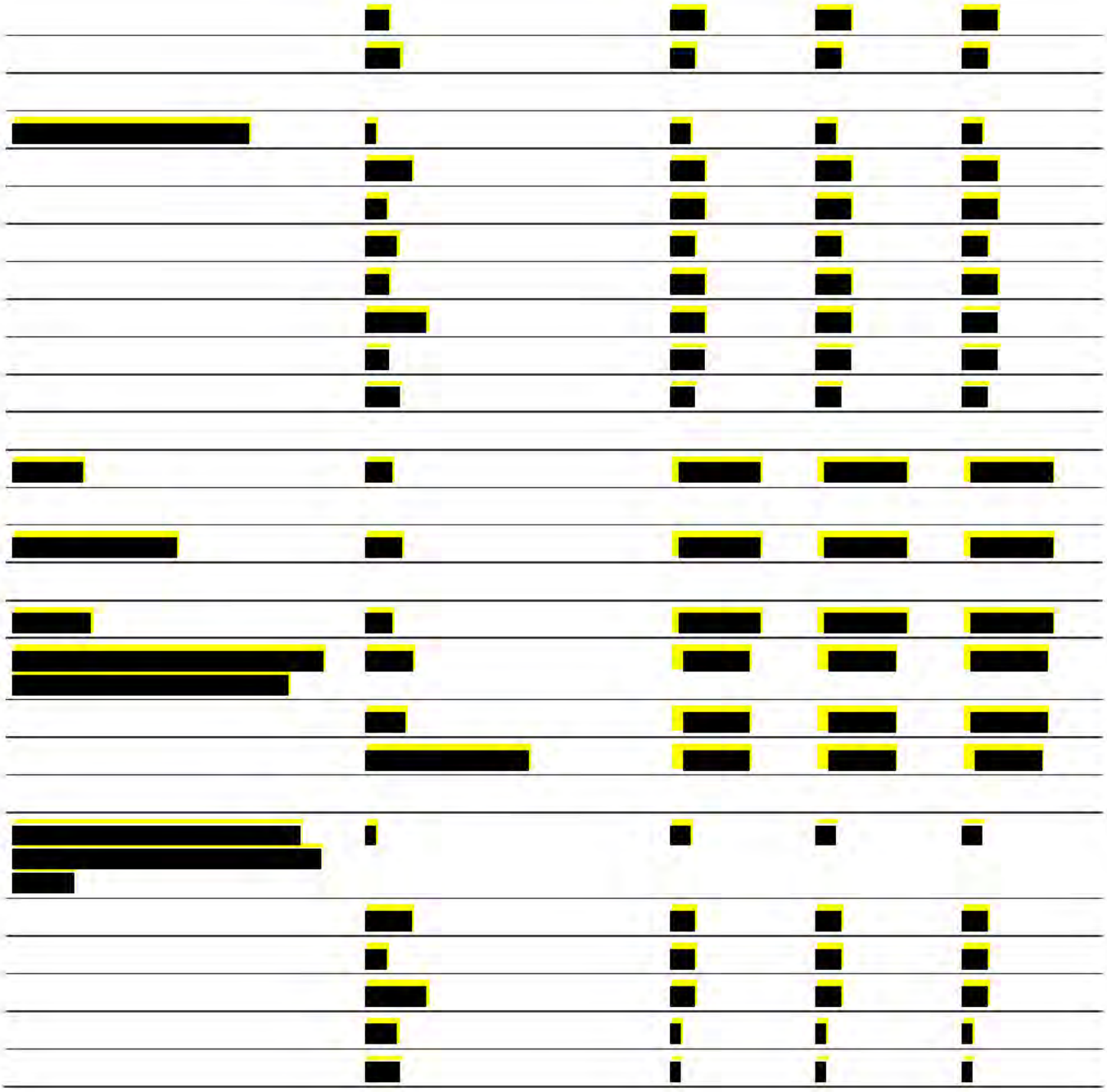


Table 32 Annual asthma exacerbation rate ratio over 48 weeks, negative binomial model, for participants with baseline eosinophil counts ≥150/µL and/or FeNO ≥25 ppb

	Annual exacerbation rate	Absolute difference from placebo	Rate ratio
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		

Table 33 Annual asthma exacerbation rate ratio over 48 weeks, negative binomial model, for participants with baseline eosinophil counts <150/µL and FeNO<ppb

	Annual exacerbation rate	Absolute difference from placebo	Rate ratio
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		

SOURCE data supported results from NAVIGATOR and PATHWAY: patients treated with tezepelumab 210 mg Q4W + SoC had a 41% reduction in exacerbations requiring hospitalisation or ER visit compared with those taking PBO Q4W + SoC, despite the reduction in OCS dose (RR: 0.59, 95%; CI: 0.19, 1.82; p=0.361). However, the overall number of exacerbations that resulted in hospitalisation or ER visit was low in both treatment arms (tezepelumab 210 mg Q4W + SoC versus PBO Q4W + SoC: 8 versus 19 events), suggesting why the result did not reach statistical significance.(18)
In SOURCE, the proportion of patients who experienced no asthma exacerbations during the 48-Week treatment period

was numerically higher in the tezepelumab 210 mg Q4W + SoC group (47.3%) compared with the PBO Q4W + SoC group (34.2%).(18)

Similar findings to NAVIGATOR and PATHWAY was also found in SOURCE in terms of longer time to first exacerbation, reduction in overall number of exacerbations irrespective of biomarker status and clinically meaningful and sustained improvement in pre-BD FEV1, and improvements in ACQ-6 was also confirmed. The OCS reduction categories were ≥90% to ≤100% reduction, ≥75% to <90% reduction, ≥50% to <75% reduction, >0% to <50% reduction and no change or any increase. The odds of reaching a category of greater percentage OCS reduction were numerically higher with tezepelumab 210 mg Q4W + SoC compared with PBO Q4W + SoC, with a cumulative OR of 1.28 (95% CI: 0.69, 2.35; p=0.434), but this did not reach statistical significance. Nevertheless, a substantial proportion of patients in the tezepelumab 210 mg Q4W + SoC (54.1%) and PBO (46.1%) arms achieved ≥90% reduction in OCS dose.[18] Analyses were also performed to investigate the effects of tezepelumab 210 mg Q4W + SoC on the primary endpoint in the SOURCE trial in subpopulations defined by baseline biomarker levels.(18) categorised percent reduction in OCS dose with tezepelumab 210 mg Q4W + SoC versus PBO Q4W + SoC was greatest in patients with baseline blood EOS ≥300 cells/µL (cumulative OR: 3.49; 95% CI: 1.16, 10.49), indicating the possible OCS-sparing effect of tezepelumab 210 mg Q4W + SoC in patients with EOS ≥300 cells/µL. Categorised percent reduction in OCS dose reduction versus placebo was also seen in patients with EOS ≥150 cells/µL (cumulative OR: 2.58; 95% CI: 1.16, 5.75), but not in patients with EOS <150 cells/µL (cumulative OR: 0.40, 95% CI: 0.14, 1.13).(18) In summary, more than half of patients treated with tezepelumab 210 mg Q4W + SoC were able to reduce their OCS dose by ≥90%, although this result was not statistically significantly different to placebo. This suggests that tezepelumab may be able to eliminate or minimise OCS use in patients who are currently on long-term OCS. This may reduce the risk of OCS-related adverse effects and long-term comorbidities and lessen the associated clinical and treatment burden.

In terms of asthma related and respiratory QoL Results from SOURCE also indicate that 62.1% of patients achieved a clinically meaningful change from baseline in AQLQ(S)+12 at Week 48 with tezepelumab 210 mg Q4W + SoC (tezepelumab 210 mg Q4W + SoC versus PBO Q4W + SoC LS Mean change from baseline: 0.94 versus 0.58; difference: 0.36; 95% CI: 0.01, 0.70). The sustained effect was seen from Week 4.

Results from the SOURCE trial regarding respiratory QoL support those seen in NAVIGATOR, with more patients treated with tezepelumab 210 mg Q4W + SoC experiencing a clinically meaningful improvement in SGRQ (i.e. a reduction of at least four points) compared to PBO Q4W + SoC at Week 48 (tezepelumab 210 mg Q4W + SoC versus PBO Q4W + SoC: 72.7% versus 49.2%; OR: 3.12; 95% CI: 1.44, 6.77; p=0.004).(18)

Safety across the clinical trials

Across the NAVIGATOR, PATHWAY and SOURCE trials, tezepelumab was well tolerated and demonstrated a similar safety profile to optimized SoC alone (Table 34).

Table 34. Safety of tezepelumab across the clinical trials

	NAVIGATOR		PATHWAY		SOURCE		
	PBO Q4W + SoC (n=531)	Teze Q4W + SoC (n=528)	PBO Q2W + SoC (n=138)	Teze + SoC (all doses) (n=412)	Teze Q4W + SoC (n=137)	PBO Q4W + SoC (n=76)	Teze Q4W + SoC (n=74)
≥1 event, n (%)	422 (79.5)	407 (77.1)	91 (65.9)	272 (66.0)	90 (65.7)	65 (85.5)	53 (71.6)
Product-related anaphylaxis, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	NAVIGATOR		PATHWAY		SOURCE		
	PBO Q4W + SoC (n=531)	Teze Q4W + SoC (n=528)	PBO Q2W + SoC (n=138)	Teze + SoC (all doses) (n=412)	Teze Q4W + SoC (n=137)	PBO Q4W + SoC (n=76)	Teze Q4W + SoC (n=74)
Product-related death, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)[a]	0 (0.0)	0 (0.0)	0 (0.0)
≥1 serious event[a], n (%)	70 (13.2)	46 (8.7)	18 (13.0)	40 (9.7)	13 (9.5)	16 (21.1)	11 (14.9)
≥1 event leading to treatment discontinuation, n (%)	19 (3.6)	11 (2.1)	1 (0.7)	5 (1.2)	2 (1.5)	2 (2.6)	2 (2.7)
Most common AEs in NAVIGATOR[c]							
Nasopharyngitis, n (%)	113 (21.3)	112 (21.2)	16 (11.6)	53 (12.9)	19 (13.9)	19 (25.0)	11 (14.9)
Upper respiratory tract infection, n (%)	84 (15.8)	58 (11.0)	-	-	-	7 (9.2)	9 (12.2)
Headache, n (%)	44 (8.3)	43 (8.1)	6 (4.3)	22 (5.3)	11 (8.0)	8 (10.5)	3 (4.1)
Asthma, n (%)	56 (10.5)	25 (4.7)	50 (36.2)	100 (24.3)	27 (19.7)	13 (17.1)	7 (9.5)
Bronchitis, n (%)	31 (5.8)	24 (4.5)	7 (5.1)	22 (5.3)	5 (3.6)	3 (3.9)	4 (5.4)

Footnotes: Colour coding used only to differentiate results from each trial. Patients were counted once for each category regardless of the number of events. [a]One patient treated with teze 70 mg + SoC died due to an event of cerebrovascular accident; this death was judged by the investigator as being related to investigational product. [b]A serious adverse event was defined as an event that resulted in death, was life threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or clinically significant disability or incapacity, was an important medical event, or resulted in a congenital anomaly or resulted in a birth defect (in the offspring of the patient). [c]Shown are the five most commonly occurring events in the group of patients who received tezepelumab in NAVIGATOR.

Abbreviations: PBO: placebo; SAS: safety analysis set; SoC: standard of care; teze: tezepelumab.

***Sources:** PATHWAY: Corren 2017;15 NAVIGATOR: 21 SOURCE: Wechsler 2022.76*

By blocking TSLP at the top of the inflammatory cascade, tezepelumab has the potential to suppress multiple inflammatory pathways and immune mechanisms, with a possible effect on the immune response to infectious agents. However, the mechanisms by which tezepelumab suppresses inflammatory pathways remains unclear.(58) Therefore, the effect of treatment with tezepelumab + SoC on the incidence of severe infections was of special interest.

Trial results show that the incidence of severe infections (defined as infections requiring treatment with systemic antiviral medications, intravenous antibiotics, or medications for helminth parasitic infection; or infections requiring permanent treatment discontinuation) was low overall and similar between the tezepelumab + SoC and PBO + SoC groups in NAVIGATOR (46 [8.7%] and 44 [8.3%] patients, respectively) and in PATHWAY (4 [2.9%] and 4 [2.9%], respectively).(21, 69) In SOURCE, the incidence of severe infections in the on-treatment period was lower in the tezepelumab + SoC group (n=4 [5.4%]) than the PBO Q4W + SoC group (n=7 [9.2%]).(76)

The incidence of cancer did not differ between the treatment groups in NAVIGATOR (n=4 in both groups, with one event being causally related to tezepelumab). (21)

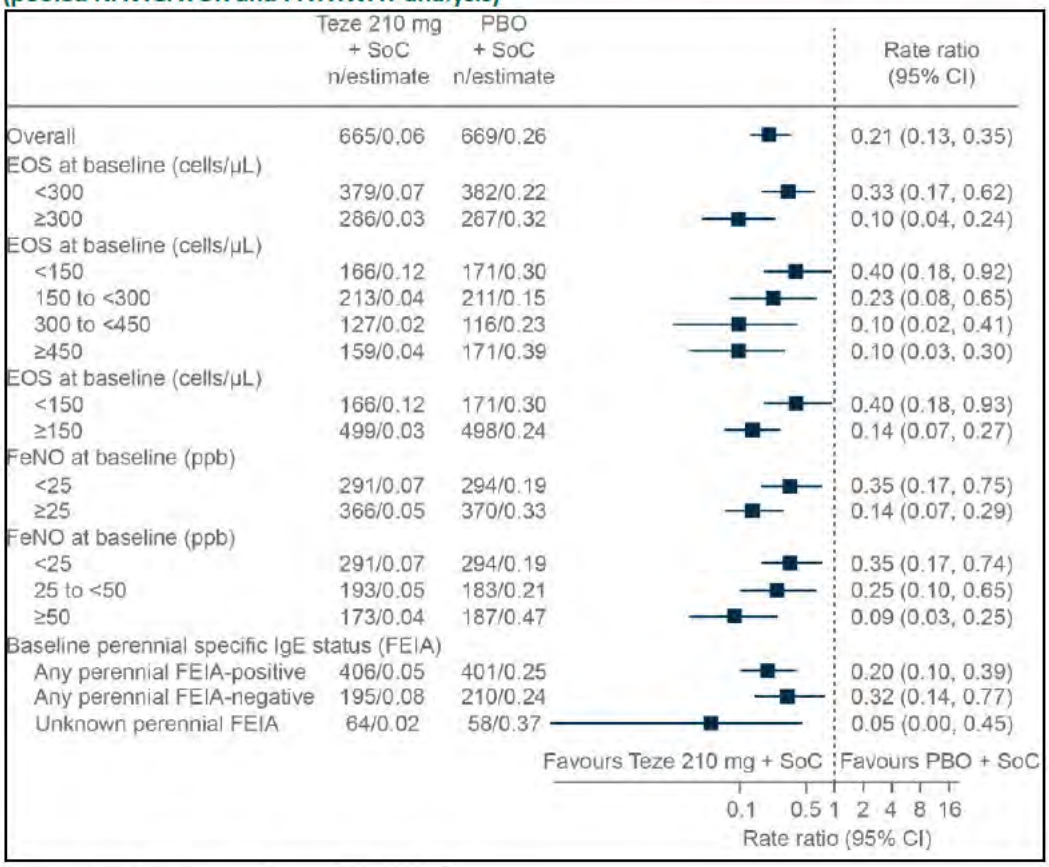
Injection site reactions occurred in 3.6% and 2.6% of patients treated with tezepelumab + SoC and PBO + SoC, respectively, in NAVIGATOR.(21)

At or after baseline, the anti-drug antibody (ADA) prevalence (defined as the proportion of patients who tested positive for ADA at any point in time) reported in the NAVIGATOR trial was 26 (4.9%) and 44 (8.3%) in the tezepelumab + SoC and PBO + SoC groups, respectively.(21)

For detailed study characteristics refer to appendix B. For baseline characteristics of patients included in each study refer to appendix C. For detailed efficacy and safety results, refer to appendices D and E.

7.1.3 Pooled analysis NAVIGATOR and PATHWAY

Figure 8. Reduction in exacerbations requiring hospitalisation or ER visit across biomarker-defined subgroups (pooled NAVIGATOR and PATHWAY analysis)



Sources AstraZeneca/Amgen Data on File 2021.(62)

Table 35 Annual asthma exacerbation rate ratio over 52 weeks, negative binomial model, for participants with baseline eosinophil counts ≥150/µL and/or FeNO ≥25 ppb (Pooled PATHWAY and NAVIGATOR)

	Annual exacerbation rate	Absolute difference from placebo	Rate ratio[a]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Table 36 Annual asthma exacerbation rate ratio over 52 weeks, negative binomial model, for participants with baseline eosinophil counts <150/µL and FeNO <25 ppb (Pooled PATHWAY and NAVIGATOR)

					Annual exacerbation rate		Absolute difference from placebo		Rate ratio[a]		
Treatment group	n	Number of events	Time at-risk (years)	Crude rate	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	p-value
[redacted]											
[redacted]											

Table 37 FEV1 (L) pre-bronchodilator change from baseline treatment comparison, mixed model for repeated measures analysis, for participants with baseline eosinophil counts ≥150/µL and/or FeNO ≥25 ppb (Pooled PATHWAY and NAVIGATOR)

		Change from baseline			Comparison with Placebo		
Timepoint	Treatment Group	n	LSMean	SE	LSMean difference	95% CI	p-value
[redacted]							

Table 38 FEV1 (L) pre-bronchodilator change from baseline treatment comparison, mixed model for repeated measures analysis, for participants with baseline eosinophil counts <150/µL and/or FeNO <25 ppb (Pooled PATHWAY and NAVIGATOR)

		Change from baseline			Comparison with Placebo		
[redacted]							

Table 39 ACQ-6 score change from baseline treatment comparison, mixed model for repeated measures analysis, for participants with baseline eosinophil counts ≥150/µL and/or FeNO ≥25 ppb (Pooled PATHWAY and NAVIGATOR)

Timepoint	Treatment Group	n	LSMean	SE	LSMean difference	95% CI	p-value

Table 40 ACQ-6 score change from baseline treatment comparison, mixed model for repeated measures analysis, for participants with baseline eosinophil counts <150/µL and FeNO <25 ppb (Pooled PATHWAY and NAVIGATOR)

		Change from baseline			Comparison with Placebo		

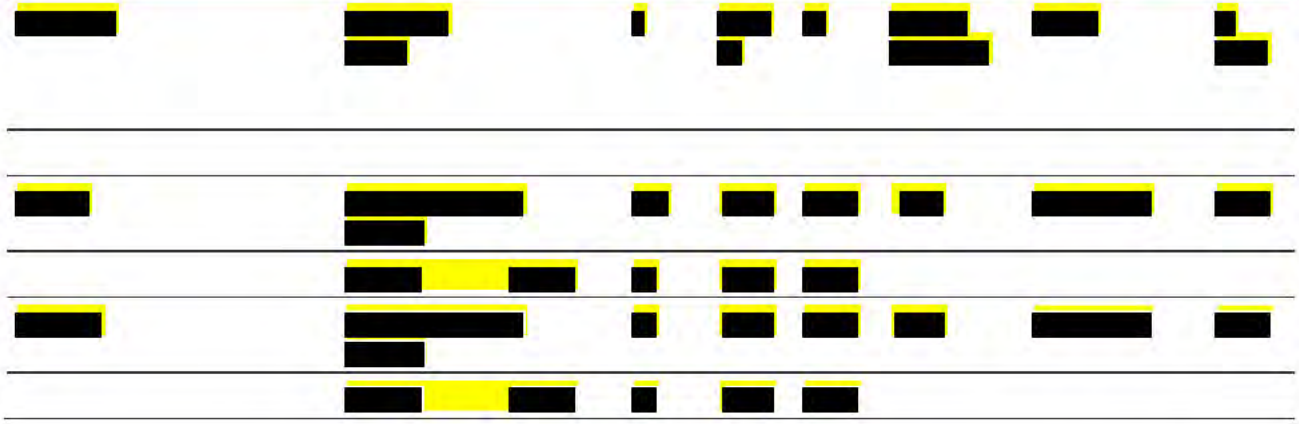


Table 41 AQLQ(S)+12 total score change from baseline treatment comparison, mixed model for repeated measures analysis, for participants with baseline eosinophil counts ≥150/µL and/or FeNO ≥25 ppb (Pooled PATHWAY and NAVIGATOR)

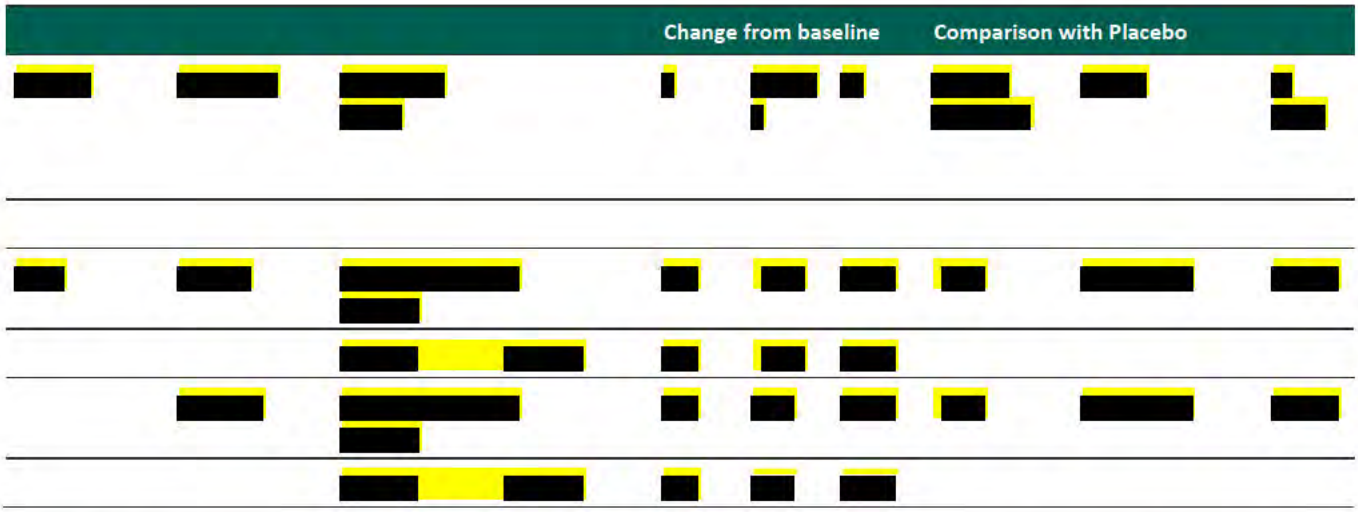
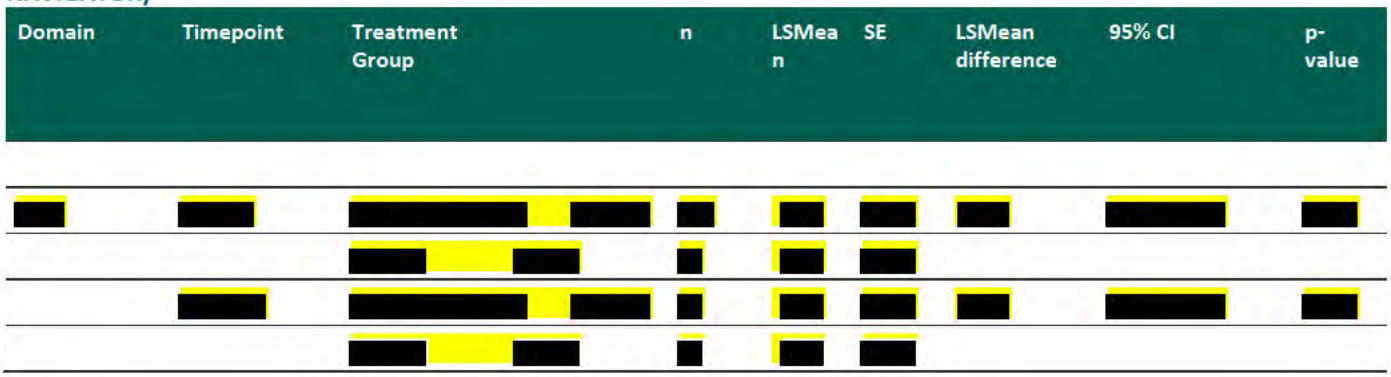


Table 42 AQLQ(S)+12 total score change from baseline treatment comparison, mixed model for repeated measures analysis, for participants with baseline eosinophil counts <150/µL and/or FeNO <25 ppb (Pooled PATHWAY and NAVIGATOR)



7.1.4 Comparative analyses of efficacy and safety tezepelumab vs SOC

As this is based on head to head results the comparative effectiveness will be described as a short summery of the results mentioned above. In the NAVIGATOR and PATHWAY trials, tezepelumab reduced AAER by up to 71% in the full study populations. This is supported by subgroup analyses conducted in NAVIGATOR, in which clinically meaningful reductions in AAER were demonstrated irrespective of EOS levels. In NAVIGATOR, tezepelumab reduced the rate of asthma exacerbations requiring hospitalisation or ER visits by 79% and exacerbations leading to hospitalisation by up to 85% compared to placebo. This result was seen regardless of EOS count and phenotype in a pooled analysis of NAVIGATOR and PATHWAY. The broad efficacy of tezepelumab is additionally supported by clinically meaningful improvements in lung function, as measured by pre-BD FEV1, in addition to PROs: asthma control (ACQ-6), symptoms (ASD) and HRQoL (AQLQ[S]+12 and SGRQ). Clinically meaningful response rates were higher with tezepelumab versus placebo across PROs. Improvements in these outcomes were observed in the full trial populations and across phenotypes, including patients with EOS <300 cells/µL. Of note, in the NAVIGATOR trial, all endpoints in the hierarchical testing procedure were met with statistical significance. The primary objective of the SOURCE trial was to evaluate the

efficacy and safety of tezepelumab in reducing OCS use in adults with OCS-dependent asthma. Amongst patients treated with tezepelumab, 54% achieved an OCS reduction of ≥90%, numerically (but not statistically significantly) higher than that amongst patients treated with placebo (46%). The placebo response was larger than observed in similar published studies of biologics, and may be attributable to the unique SOURCE study design, which included a long OCS reduction phase and the permission for multiple down-titration attempts. In SOURCE, treatment with tezepelumab reduced exacerbations and improved lung function, asthma control and HRQoL, supporting the favorable efficacy of tezepelumab observed in NAVIGATOR and PATHWAY.

7.2 Efficacy and safety of tezepelumab compared to other biologics

7.2.1 Relevant studies

Table 43 List of RCTs assessing the efficacy and safety of relevant biologics included in the ITC feasibility assessment(11, 12, 63-76)

Benralizumab	Dupilumab	Mepolizumab	Omalizumab	Reslizumab	Tezepelumab
• SIROCCO (2016) • CALIMA (2016) • ZONDA (2017) • ALIZE (2018) • ANDHI (2020) • SOLANA (2020)	• Wenzel (2016) • LIBERTY ASTHMA QUEST (2018) • LIBERTY ASTHMA VENTURE (2018) • Wechsler (2021)	• MENSA (2014) • SIRIUS (2014) • MUSCA (2017)	• Ayres (2004) • Holgate (2004) • INNOVATE (2005) • NCT00567476 (2007) • Ohta (2009) • Chanez (2010) • EXALT (2011) • Hanania (2011) • Bardelas (2012) • Hoshino (2012) • QUALITX (2012) • Busse (2013) • NATAIR (2013) • Pasha (2014) • Li (2016) • Mukherjee (2019)	• Castro (2011) • Castro (2015) • Bjermer (2016) • Corren (2016)	• PATHWAY (2017) • NAVIGATOR (2020) • SOURCE (2020)

Abbreviations: ITC = indirect treatment comparison; RCT = randomized controlled trial.

7.2.2 Efficacy and safety – results per study

All studies listed in Table 43 above was included in the ITC feasibility assessment, however only the dupilumab studies will be described in detail in the following sections, as dupilumab is the main comparator based on arguments listed in sections above. All the biologic treatments included in the ITC has been assessed by the DMC in the current treatment guideline, why this work will not be repeated here. For more details see the comparative analysis and Appendix A-F.
For dupilumab, we hereby describe the studies: QUEST, Wenzel and Wechsler and VENTURE:

- QUEST is a randomized, double-blind, placebo-controlled phase III study, that lasted for 52 weeks. Included patients had severe uncontrolled asthma with at least one exacerbation last year that required treatment with moderate or

high-dose ICS and LABA. The included patients were randomized for treatment with either 200mg or 300mg dupilumab every other week.
Results: Patients receiving either 200mg or 300mg dupilumab every two weeks, statistically significantly reduced the severe asthma exacerbations compared to patients in the placebo arm. The reduction were greater in patients with type 2 inflammatory biomarkers. Better lung function and asthma control was also observed in patients treated with dupilumab.

- VENTURE is randomized, double-blind, placebo-controlled phase III study, that lasted for 28 weeks. VENTURE evaluated the efficacy of dupilumab in reducing the use of OCS as maintenance treatment.
  Results: The median decrease in the daily OCS dose was statistically significant for patients on dupilumab compared with the patients in the placebo arm.

- Wenzel et al. is a randomized, double-blind, placebo-controlled, parallel-group, pivotal phase 2b clinical trial at 174 study sites across 16 countries. The trial lasted 24-weeks and the population included adults 18+ with an asthma diagnosis.
  Results: Dupilumab increased lung function and reduced severe exacerbations in patients with uncontrolled severe asthma compared to standard therapy alone.

- Wechsler et al: is an open label extension study in 362 hospitals and clinical centers across 27 countries. The study assessed the efficacy and safety of dupilumab every second week up to 96 weeks in patients 12+. Patients was recruited from earlier asthma studies (phase 2A EXPEDITION, phase 2B DRI [P2b], phase 3 QUEST, or VENTURE) and followed up to 148 weeks.
  Results: The study showed that the efficacy and safety of dupilumab persisted when treatment was extended up to 148 weeks.

7.2.3 Comparative analyses of efficacy and safety tezepelumab vs other biologics

Currently approved biologic treatments in asthma are indicated for patients with severe asthma, however, no head-to-head trials have compared the efficacy of Tezspire with these biologics. Indirect Treatment Comparisons (ITCs) were therefore performed to compare Tezspire with relevant biologics for the treatment of severe uncontrolled asthma (covering the indications of approved biologics).(21, 22) A clinical systematic literature review (SLR) were conducted. The included studies in the SLR were observed to have too large clinical and methodological differences in patient populations, outcome measures, and study design to be able to make an ITC with all comparators at the same time. Thus, a subsequent network meta-analysis (NMA) was conducted to evaluate the comparative effectiveness of the comparators with a common placebo arm. (77)

Method of synthesis

All primary NMAs were conducted using the intent-to-treat (ITT) populations of relevant RCTs. Reduction in AAER and reduction in AAER leading to hospitalization were assessed at various time-points across the included RCTs (ranged from week 12 to week 52).

Five outcomes, informed by clinical importance, payer relevance and availability in comparator publications, were considered in the NMA:

- Reduction in AAER (count)
- Reduction in exacerbations leading to hospitalization (count)
- Change from baseline in ACQ score (continuous)

- Change from baseline in pre-bronchodilator FEV_1 (continuous)
- Change from baseline in the OCS dose by predefined mutually exclusive reduction categories (reduction of ≥50%, 50–75%, 75–90%, 90–100%).(ordinal)

For each of the five clinical outcomes, evidence networks were developed and a Bayesian NMA was performed according to established methods (based on those outlined in the National Institute for Health and Care Excellence [NICE] Decision Support Unit [DSU] Technical Support Documents [TSDs]).(78)
Subgroup analyses were undertaken in key clinically relevant subpopulations based on blood EOS, FeNO, number of prior exacerbations and presence of allergic asthma, reflecting the diversity of approved indications and reimbursement criteria for the comparator products. In addition, subgroup analyses allowed comparison of the effectiveness of biologics in populations with similar patient characteristics (i.e. asthma control-related characteristics and biomarkers). Further details on the methodology of the NMA, including details on the included studies, can be found in Appendix A-F.(79)

Results from the comparative analysis
For AAER reduction (minimal clinically important difference [MCID]: ≥20% reduction or RR ≤0.80), tezepelumab demonstrated favorable effectiveness compared with all comparators in the NMA. For reduction in exacerbations leading to hospitalisation, no MCID is available but results numerically favored tezepelumab compared with all comparators in the NMA with any reduction in this outcome anticipated to be meaningful.
For the outcomes of change from baseline in ACQ score and in FEV1, results from the NMA were mixed. These results were not clinically important (MCID for ACQ score and FEV1: 0.5 points and 0.2 L, respectively) and thus demonstrated the comparable effectiveness of tezepelumab with other biologics;
For categorised percent reduction in OCS dose (no MCID available), results of the NMA of the overall population favored the other biologics. However, the results of the NMA of the subgroup with EOS >300 cells/µL, which offer more targeted comparisons, suggested favorable effectiveness with tezepelumab. In the NMA of the subgroup with EOS >150 cells/µL, tezepelumab performed comparably with other biologics.

Overall, the NMA subgroup results demonstrates a numerically favorable effect on categorised percent reduction in OCS dose for tezepelumab versus other currently approved biologics. These results highlight the favorable efficacy of tezepelumab as a treatment for severe, uncontrolled asthma patients, demonstrating numerical superiority or comparable effectiveness with other biologics in most endpoints and subgroups.
Data across the clinical trials and indirect treatment comparisons demonstrate that tezepelumab is the only therapy to provide an effective and tolerable treatment option across all patients with severe, uncontrolled asthma, irrespective of phenotype or biomarker status. An overview of the pairwise comparison from the NMA can be seen in Table 44.

Table 44. Pairwise comparisons from the NMA between tezepelumab and other currently approved biologics

Outcome	Outcome type	MCID (favouring tezepelumab)	Comparator (reference) treatment					
			Benralizumab	Dupilumab 200 mg	Dupilumab 300 mg	Omalizumab	Mepolizumab	Reslizumab
Reduction in AAER	RR (95% CrI); <1 favours tezepelumab	≤0.80 (20% reduction)	0.63 (0.35, 1.09)	0.84 (0.45, 1.56)	0.84 (0.45, 1.56)	0.6 (0.35, 1.01)	0.82 (0.43, 1.49)	0.82 (0.43, 1.49)
Reduction in exacerbations leading to hospitalisation	RR (95% CrI); <1 favours tezepelumab	NA[a]	0.35 (0.08, 1.16)	0.36 (0.07, 1.59)	**NA**	0.40 (0.10, 1.55)	0.54 (0.13, 2.00)	0.29 (0.07, 1.08)
ACQ score	LSMean difference in CfB (95% CrI); <0 favours tezepelumab	≤ -0.5	-0.01 (-0.30, 0.28)	0.04 (-0.29, 0.36)	-0.06 (-0.38, 0.27)	0.16 (-0.19, 0.51)	0.1 (-0.24, 0.45)	-0.06 (-0.34, 0.27)
pre-BD FEV_1 (L)	LSMean difference in CfB (95% CrI); >0 favours tezepelumab	≥ +0.2 L	0.02 (-0.07, 0.11)	-0.01 (-0.10, 0.08)	0.0 (-0.09, 0.09)	0.08 (-0.01, 0.18)	0.02 (-0.07, 0.12)	0.01 (-0.08, 0.09)
OCS dose reduction by ≥50%	OR (95% CrI); >1 favours tezepelumab	NA	0.38 (0.14 to 1.07)	NA	0.36 (0.14 to 0.93)	NA	0.54 (0.20 to 1.47)	NA
OCS dose reduction by 50–75%[b]	OR (95% CrI); >1 favours tezepelumab	NA	0.37 (0.16 to 0.85)	NA	0.42 (0.19 to 0.93)	NA	0.54 (0.23 to 1.30)	NA
OCS dose reduction by 75–90%[b]	OR (95% CrI); >1 favours tezepelumab)	NA	0.38 (0.16 to 0.86)	NA	0.42 (0.20 to 0.93)	NA	0.54 (0.24 to 1.30)	NA
OCS dose reduction by 90–100%[b]	OR (95% CrI); >1 favours tezepelumab	NA	0.38 (0.16 to 0.86)	NA	0.42 (0.19 to 0.93)	NA	0.54 (0.23 to 1.30)	NA

Footnotes: *No results were statistically significant at p=0.05.[a]No MCID is available for the reduction in exacerbations leading to hospitalisation, but any reduction may be considered clinically relevant.[b]The reciprocal of odds ratios with tezepelumab as the comparator treatment have been calculated to present odds ratios with the other biologics as the comparator treatment.*

Abbreviations: *ACQ: Asthma Control Questionnaire; BD: bronchodilator; CfB: change from baseline; CrI: credible interval; FEV_1: forced expiratory volume in one second; LSMean: least squares mean; MCID: clinically important difference; NA: no data available; NMA: network meta-analysis; OCS: oral corticosteroid; OR: odds ratio; RR: rate ratio; TBC: to be confirmed.*

Source: *AstraZeneca/Amgen Data on File 2021.(79)*

[redacted]

No subgroup analyses were conducted for AAER leading to hospitalizations due to the lack of available data.

[redacted]

For the outcome of change from baseline in the OCS dose, the were no statistically significant difference between tezepelumab and the other currently approved biologics. When studying the change from baseline in OCS dose by ≥50%, both tezepelumab and dupilumab showed statistically significant improvements compared to mepolizumab.

Table 45 Overview of subgroup analysis results.

Subgroup of Interest	Definition	Findings/comparisons with primary analysis
Reduction in AAER		
High blood EoS level	≥150 cells/µL	Tezepelumab was statistically significantly better than omalizumab (RR 0.63 (95%CI 0.43 to 0.94)) and benralizumab (RR 0.63 (95%CI 0.49 to 0.82)).
Low blood EoS level	<150 cells/µL	Tezepelumab was statistically significantly better than dupilumab 300mg (RR 0.55 (95%CI 0.39 to 0.79)).
Change from baseline in ACQ Score		
High blood EoS level	≥150 cells/µL	Tezepelumab and mepolizumab were statistically significantly better than benralizumab (RR -0.23 (95%CI -0.40 to -0.04) and (RR -0.32 (95%CI -0.53 to -0.11), respectively).
Low blood EoS level	<150 cells/µL	No statistically significant differences between biologics.
Change from baseline in pre-bronchodilator FEV		
High blood EoS level	≥150 cells/µL	No statistically significant differences between biologics.
Low blood EoS level	<150 cells/µL	No statistically significant differences between biologics
Change from baseline in the OCS dose		
Change from baseline in OCS dose by ≥50%, ≥75%, or ≥90%		
High blood EoS level	≥150 cells/µL	No statistically significant differences between biologics.
Change from baseline in OCS dose by ≥50%		
High blood EoS level	≥150 cells/µL	No statistically significant differences between biologics.

Abbreviations: AAER = annualized asthma exacerbation rate; EoS = eosinophil.

Safety comparison

Statistical indirect comparisons of adverse events were not performed. There are several reasons why a statistical comparison may be challenging to perform, but most importantly a numerical comparison of adverse events will not necessarily give clinically important information. For instance, a grade 3 ADR that can be treated symptomatically will have a different clinical importance than a grade 3 ADR for which there is no treatment. It is also of importance to consider whether the side effect leads to treatment discontinuation or not. However, when comparing treatment discontinuation frequencies, one should keep in mind that discontinuation often is made based on a holistic medical evaluation, and that it may differ between studies how one defines the main leading cause for discontinuation. A statistical/numerical comparison of discontinuations due to ADRs may therefore be skewed. Finally, a product's safety profile is continually updated as a marketed product is used for alle marketed indications as well as off-label treatment, and both frequencies for already identified adverse events and new adverse events may be included in updated in the SmPCs postmarketing.

Instead of a statistical comparison, AstraZeneca have therefore performed a simplified evaluation of the clinical importance of the safety profiles based on information from the relevant SmPCs.

Table 46 Summarise of Frequencies and Adverse Reactions for the biologics included in the ITCs

	Frequencies and Adverse Reactions				
MedDRA System Organ Class	Tezspire (80)	Dupixent (81)	Fasenra (82)	Nucala (83)	Xolair (84)
Infections and infestations	Common: Pharyngitis[a]	Common: Conjunctivitis[b] Oral herpes[b]	Common: Pharyngitis[a]	Common: Lower respiratory tract infection Urinary tract infection Pharyngitis	Uncommon: Pharyngitis Rare: Parasitic infection
Blood and lymphatic system disorders	N/A	Common: Eosinophilia	N/A	N/A	Not known: Idiopathic thrombocytopenia, including severe cases
Immune system disorders	N/A	Uncommon: Angioedema[c] Rare: Anaphylactic reaction Serum sickness reaction Serum sickness-like reaction	Common: Hypersensitivity reactions[d] Not known: Anaphylactic reaction	Common: Hypersensitivity reactions (systemic allergics)[e] Rare: Anaphylactic reaction[f]	Rare: Anaphylactic reaction, other serious allergic conditions, antiomalizumab antibody development Not known: Serum sickness, may include fever and lymphadenopathy
Nervous system disorders	N/A	N/A	Common: Headache	Very common: Headache	Common: Headache[g] Uncommon: Syncope, paraesthesia, somnolence, dizziness[h]
Vascular disorders	N/A	N/A	N/A	N/A	Uncommon: Postural hypotension, flushing
Eye disorders	N/A	Common: Conjunctivitis allergic[i] Uncommon: Keratitis[i, c]	N/A	N/A	N/A

		Blepharitis[i, j] Eye pruritus[i, j] Dry eye[i, j] Rare: Ulcerative keratitis[i, j, c]			
Respiratory, thoracic and mediastinal disorders	N/A	N/A	N/A	Common: Nasal congestion	Uncommon: Allergic bronchospasm, coughing Rare: Laryngoedema Not known: Allergic granulomatous vasculitis (i.e. Churg-Strauss syndrome)
Gastrointestinal disorders	N/A	N/A	N/A	Common: Abdominal pain upper	Common: Abdominal pain upper[k, h]
Skin and subcutaneous tissue disorders	Common: Rash[l]	Uncommon: Facial rash[c]	N/A	Common: Eczema	Uncommon: Photosensitivity, urticaria, rash, pruritus Rare: Angioedema Not known: Alopecia
Musculoskeletal and connective tissue disorders	Common: Arthralgia	Common: Arthralgia[c]	N/A	Common: Back pain	Common: Arthralgia[m] Rare: Systemic lupus erythematosus (SLE) Not known: Myalgia, joint swelling
General disorders	Common:	Common:	Common:	Common:	Very common:

and administration site conditions	Injection site reactions	Injection site reactions (includes erythema, oedema, pruritus, pain, and swelling)	Pyrexia Injection site reaction	Administration-related reactions (systemic non allergic)[n] Local injection site reactions Pyrexia	Pyrexia[k] Common: Injection site reactions such as swelling, erythema, pain, pruritus Uncommon: Influenza-like illness, swelling arms, weight increase, fatigue

[a] *Pharyngitis was defined by the following grouped preferred terms: 'Pharyngitis', 'Pharyngitis bacterial', 'Viral pharyngitis', 'Pharyngitis streptococcal'*
[b] *Eye disorders and oral herpes occurred predominately in atopic dermatitis studies.*
[c] *From postmarketing reporting.*
[d] *Hypersensitivity reactions were defined by the following grouped preferred terms: 'Urticaria', 'Papular urticaria', and 'Rash'*
[e] *Systemic reactions including hypersensitivity have been reported at an overall incidence comparable to that of placebo in the severe eosinophilic asthma studies*
[f] *From spontaneous post marketing reporting*
[g] *Very common in children 6 to <12 years of age*
[h] *Common in nasal polyp trials*
[i] *Eye disorders and oral herpes occurred predominately in atopic dermatitis studies.*
[j] *The frequencies for eye pruritus, blepharitis, and dry eye were common and ulcerative keratitis was uncommon in atopic dermatitis studies*
[k] *In children 6 to <12 years of age*
[l] *Rash was defined by the following grouped preferred terms: rash, rash pruritic, rash erythematous, rash maculo-papular, rash macular*
[m] *Unknown in allergic asthma trials*
[n] *The most common manifestations associated with reports of systemic non-allergic administrationrelated reactions from patients in the severe eosinophilic asthma studies were rash, flushing and myalgia; these manifestations were reported infrequently and in <1% of patients receiving mepolizumab 100 mg subcutaneously.*

Overall, AstraZeneca evaluates that tezepelumab's safety profile as presented in the SmPC is in line with profiles for the other biological drugs, both when it comes to type and frequencies of adverse events. The safety profiles show some differences that may be of clinical importance to the individual patient, highlighting that it is important that the specialists have several medicinal drugs to choose between when optimizing the patient's treatment.

Conclusion of comparative effectiveness

Overall

In the comparative efficacy analysis tezepelumab has demonstrated efficacy across phenotypes and irrespective of biomarkers, as evidenced by direct clinical evidence compared to SoC (GINA Step 4-5 treatment with medium-high dose ICS with another controller or maintenance OCS)(23), as well as comparable effectiveness with other biologics observed in the ITCs. This consolidates its positioning as the preferred first-line biologic across all patients with severe, uncontrolled asthma.

Tezepelumab vs other biologics

The presented NMAs support the conclusion that biologic interventions for severe uncontrolled asthma are associated with significantly improved AAER, AAER leading to hospitalization, ACQ score, FEV_1 and OCS reduction as compared with placebo.

Additionally, the results suggest that there are no clear differences between biologic comparators for any of the outcomes. However, these results should be interpreted with caution given the extent of clinically important heterogeneity in patient populations and trial methods across studies.

The impact of these sources of heterogeneity was explored in subgroup analyses, showing advantages of tezepelumab, especially in the reduction of AAER.

Other ITCs were preformed (STC and MAIC) which supported the result of the NMA, why not presented here. Both analysis can be shared upon request.

7.3 Update: new long term safety data study published (DESTINATION)

- DESTINATION was a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group long-term extension study designed to evaluate the long-term safety, tolerability, and efficacy of tezepelumab in adult and adolescent patients with severe, uncontrolled asthma who had completed treatment from the 52-week NAVIGATOR study or the 48-week SOURCE study (n=951).
- The primary endpoints were exposure-adjusted incidence rates of AEs and SAEs over 104 weeks. The secondary endpoint was annualized adjusted exacerbation rate (AAER) over 104 weeks.
- Tezepelumab was well tolerated over 104 weeks, with lower rates of overall AEs, SAEs, and AEs leading to discontinuation compared with placebo.
- Tezepelumab resulted in sustained reductions in exacerbations, including those associated with hospitalization or ED visit over 104 weeks. Furthermore, tezepelumab reduced AAER irrespective of baseline biomarker level or perennial allergy status.
- Early and sustained reductions in BEC and FeNO levels were observed in patients who were in the randomized tezepelumab group compared with those in the randomized placebo group, as well as a progressive reduction in serum total IgE levels, which was sustained to Week 104. (85)

Conclusion from DESTINATION

Cardiac Disorders AEs

- In the overall pooled patient population, the on-study incidence of AEs categorized as cardiac disorders were similar between the randomized tezepelumab group (incidence per 100 patient-years, 2.76) and the randomized placebo group (incidence per 100 patient-years, 2.99); difference -0.23, 95% CI -1.81 to 1.24 (85)
- Cardiac Disorders SAEs
  - In the overall pooled patient population, the on-study incidence of SAEs categorized as cardiac disorders was higher in patients treated in the all tezepelumab group versus randomized placebo group (exposure-adjusted incidence rate per 100 patient years of 1.30 versus 0.23, respectively)(85)
  - No pattern in either the cause of the cardiac SAEs or the timing of the cardiac SAEs in relation to study drug administration was identified; event types varied (e.g., cardiac arrhythmias, coronary artery disease, heart failures, and myocardial disorders)(85)
  - None of the cardiac SAEs were considered causally related to tezepelumab by the investigators or masked, independent adjudication committee members, nor were these imbalances observed in previous multidose studies of tezepelumab of up to 1 year of treatment(1, 85, 86)
  - All patients who experienced a cardiac disorder SAE had at least 2 risk factors at baseline and 44% of patients (8 of 18) had a cardiac disorder at baseline that may have contributed to these events
  - A patient population at risk of these events has not been identified(85)

- Adjudicated Major Adverse Cardiovascular Events

- Major adverse cardiovascular events (MACE) were evaluated during the study by a masked, independent adjudication committee.
  - Potential MACE events (stroke, myocardial infarction, or unstable angina) were reviewed by the masked, independent adjudication committee. MACE events that resulted in death were categorized as cardiovascular deaths within the MACE category.(85) Details related to adjudicated MACE events are provided in the supplement.
- Rates of MACE per 100 patient-years were 0.65 for all tezepelumab group versus 0.46 for the randomized placebo group, with an incidence rate difference per 100 patient years of 0.19 (95% CI, -0.58 to 0.85).(85)
- None of the MACE events were considered causally related to tezepelumab by the investigators or blinded independent adjudication committee members. (85)

8. Health economic analysis

At present, there are five biologic therapies for patients with evidence of allergic or eosinophilic asthma recommended for biologic treatment by the DMC treatment guideline (dupilumab, benralizumab, omalizumab, reslizumab and mepolizumab). However, there are patient populations outside this recommendation with severe asthma that are not eligible for the current biologic treatments but where tezepelumab has proven to be an effective treatment. Thus, AstraZeneca provides two analyses to conclude the economic value of tezepelumab.

Cost-minimization analyses were conducted for type 2 asthma patients that are recommended for biologic treatment in the current DMC guidelines (Table 47). This patents population includes patients with elevated type 2 inflammatory biomarkers (EOS, FeNO, and severe allergy) and the comparator was dupilumab.

Cost-effectiveness analyses were conducted for type 2 low asthma that is not recommended for biologic treatment in the current DMC guidelines (Table 47). Since there is no available biologic therapy for this population, AstraZeneca considers SoC of high-dose ICS and LABA as the comparator.

Table 47. Overview of populations and analyses in the Economic value section.

Subpopulation	Analysis	Comparator
Patients with high EOS (≥150) AND/OR High FeNO (≥25)	CMA	Dupilumab
Patients with severe allergic asthma	CMA	Dupilumab
Patients with type 2 low asthma (low EOS (<150) AND low FeNO (<25))	CUA	SoC

Cost-minimization analyses

Based on the indirect treatment comparison (ITC) method conducted, tezepelumab has a comparable effect to existing reimbursed biologic treatments as add-on therapies in addition to GINA LV step 5, high-dose ICS and other controllers for patients with evidence of allergic or eosinophilic severe asthma in Denmark (dupilumab, benralizumab, mepolizumab, reslizumab, and omalizumab). On this basis, AstraZeneca concludes that a full cost-effectiveness analysis is not required, instead, a cost-minimization analysis (CMA) was conducted for patients with type 2 high asthma (EOS≥ 150 AND/OR FeNO≥25) and for patients with severe allergic asthma. AstraZeneca has analyzed the severe asthma

treatment guideline made by the DMC with respect to identifying comparators. Overall, the DMC has deemed the clinical efficacy between dupilumab, benralizumab, mepolizumab, reslizumab and omalizumab to be comparable/equal where indications overlap. Based on this, AstraZeneca regards dupilumab as the most relevant comparator to tezepelumab. Thus, the cost-minimization analysis is conducted on a comparison between tezepelumab and dupilumab for the patients that are recommended for biologic treatment in the current DMC guidelines (Table 47).

The CMA analysis was based on the same assumptions as the cost-effectiveness model presented below, but only costs were included. The equal effect between Tezepelumab and Dupilumab was assumed, thus all effect data for Dupilumab were set to the same as Tezepelumab.

Cost-effectiveness analyses

The aim of the health economic modelling was to describe the cost-effectiveness of treatment with tezepelumab compared to SoC for T2 low asthma subpopulation that are not recommended for biologic treatment in the current DMC guidelines (Table 47). A 5 health state, cohort-based, Markov model was conducted to assess the incremental cost-effectiveness of tezepelumab compared to SoC from a societal perspective. The model used a cycle length of 4 weeks to align with the timing of patient's treatment and disease progression, as well as recurring costs. The time horizon in the model was life-time, with a maximum of 60 years, to capture all significant differences in costs and health effects between treatment with tezepelumab in comparison to SoC. Costs are expressed in Danske Kroner (DKK) at the 2022 year prices. When required, costs were converted to 2022 prices using the consumer price index (CPI) available from Statistics Denmark (87). Health effects were estimated in terms of quality-adjusted life years (QALYs). According to DMC guidelines for the submission, a 3.5% discount rate during the first 35 years and a discount rate of 2.5% during years 36 to 70 were applied in the base case for both costs and health effects (QALYs).

Cost-effectiveness model design

The cost-effectiveness model was designed to include two important clinical dimensions of asthma; *symptom control* and *exacerbation status*. Patients with severe, uncontrolled asthma may experience a greater symptom burden and lower HRQoL than those with controlled asthma. They are also at higher risk of experiencing an exacerbation, and a proportionally greater number of these exacerbations are predicted to require an accident and emergency (A&E) visit or hospitalization (rather than OCS bursts); this may further reduce HRQoL and necessitate additional healthcare resource use. To comprehensively reflect the disease progression of patients with severe asthma, the cost-effectiveness model incorporated both asthma control status and exacerbation events explicitly. The Markov model is illustrated in Figure 9. Patients enter the Markov model either in a tezepelumab or SoC cohort, then the cohorts enter within or without OCS cohorts (Figure 9A).

Based on the tezepelumab label, patients enter the Markov model in an uncontrolled asthma health state, defined by the ACQ-6 score equal to and above 1.5, and can then transition between controlled asthma health state, defined by the ACQ-6 score below, and the remaining health states, as shown by the arrows in Figure 9B. A cut-off of 1.5 for the ACQ-6 score was used since this was the definition used in the NAVIGATOR pivotal trial. Also, this is the definition of uncontrolled and controlled asthma used in previous cost-effectiveness models of severe asthma (88-90)

The remaining health states are defined as follows:

- Exacerbation health states:
    - Controlled Exacerbation: An severe exacerbation event in controlled asthma patients
    - Uncontrolled Exacerbation: An severe exacerbation event in uncontrolled asthma patients

- Severe exacerbation events:
    - Burst of OCS for at least 3 consecutive days
    - An emergency room or A&E visit
    - Hospitalisation
- Death:
    - Mortality includes all-cause mortality and exacerbation related mortality.

Patients who enter the model in a biologic cohort can transition to SoC only through natural attrition (discontinuation) or at a response assessment (a single pre-defined timepoint when clinicians determine whether patients should continue on their biologic treatment based on their prior response to treatment; this is assumed to occur at Week 52 in the base case analysis.

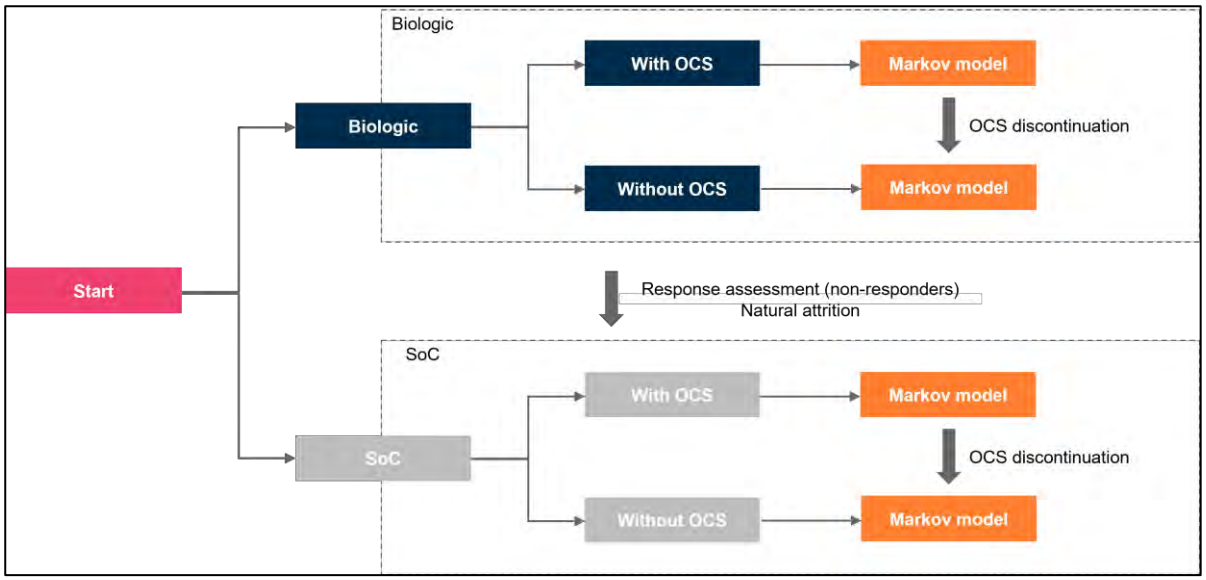
The assessment week in the model is a single timepoint where clinicians determine whether patients should continue using a biologic treatment based on their response to the treatment prior the response week. Thus, prior to the assessment week, both non-responders and responders are included within the population on each biologic. Conversely, after the assessment week, only responders are included. The response week is set to week 52 in the model.

Groups	Definition
Pre assessment with OCS	Biologic treatment with maintenance OCS at baseline before the assessment week
Pre assessment without OCS	Biologic treatment without maintenance OCS at baseline before the assessment week
Post assessment with OCS	Biologic treatment with maintenance OCS at baseline after the assessment week
Post assessment without OCS	Biologic treatment without maintenance OCS at baseline after the assessment week

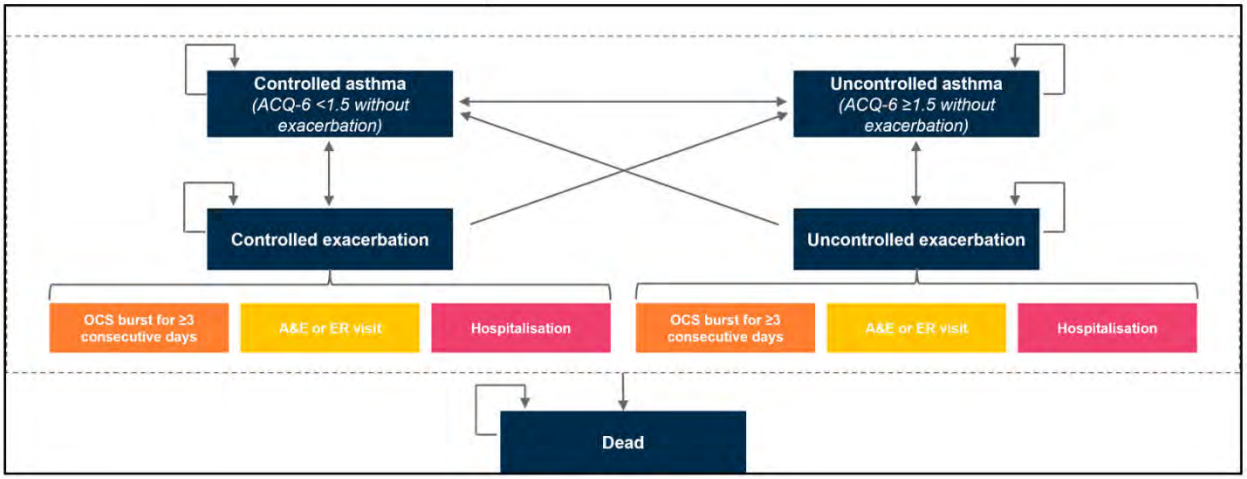
The model was developed in Microsoft Excel® 2102.

Figure 9. Model structure used for the 5 health state Markov model

(A) Patient flow through model based on treatment arm and OCS status



(B) Health states in the 5-state Markov model, and the allowed transitions between them



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

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

The input data used for the base case was mainly derived from the pivotal trial NAVIGATOR (16). A summary of included clinical inputs is presented in Table 50.

Table 48. Estimates applied in the health economic model.

Variable	Value	Source
Patient characteristics		
Mean starting age (years)		
Type 2 low asthma (SE)	[redacted]	NAVIGATOR (16)
Proportion males (%)		
Type 2 low asthma (SE)	[redacted]	NAVIGATOR (16)
Discontinuation		
Natural discontinuation (4-weekly probability) (SE)	[redacted]	NAVIGATOR (16)
Probability of discontinuation at 52-week assessment		
Type 2 low asthma (SE)	[redacted]	NAVIGATOR (16)
Quality of life (EQ-5D-5L)		
[redacted]	[redacted]	NAVIGATOR (16) and SOURCE (91)
[redacted]	[redacted]	
[redacted]	[redacted]	Lloyd et al (92)
[redacted]	[redacted]	
[redacted]	[redacted]	

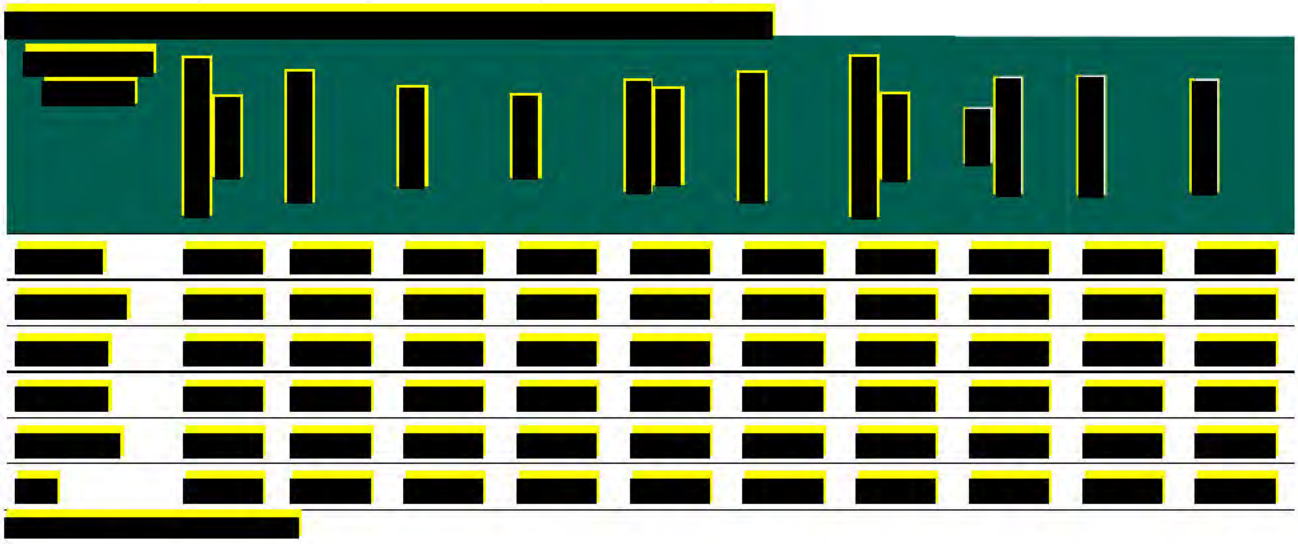
OCS sparing

One expected treatment effect for interventions provided to patients with severe asthma is a reduction of OCS use both in terms of overall dose reduction but also the stopping of OCS entirely. In order to capture this treatment effect, the model initially defines the proportion of patients who are using OCS at baseline. For the T2 low subpopulation, [redacted] of the patients were on maintenance OCS use at baseline with a mean dose of [redacted] mg per day. The OCS sparing week was set to 52 in the model. Then, at the OCS sparing week, the model has separate parameters to define the proportion of patients who discontinue OCS, and those who achieve the following dose reductions. The OCS sparing data are collected from SOURCE for the specific subpopulations.

OCS-related adverse events

OCS-related adverse events are modelled in terms of their impact on both HRQoL and costs. In order to apply these costs and quality of life decrements, and effects of OCS sparing, the frequency of adverse events based on OCS dose are included in the model (annual probabilities summarized in Table 51, which are converted into 4-week probabilities within the model).

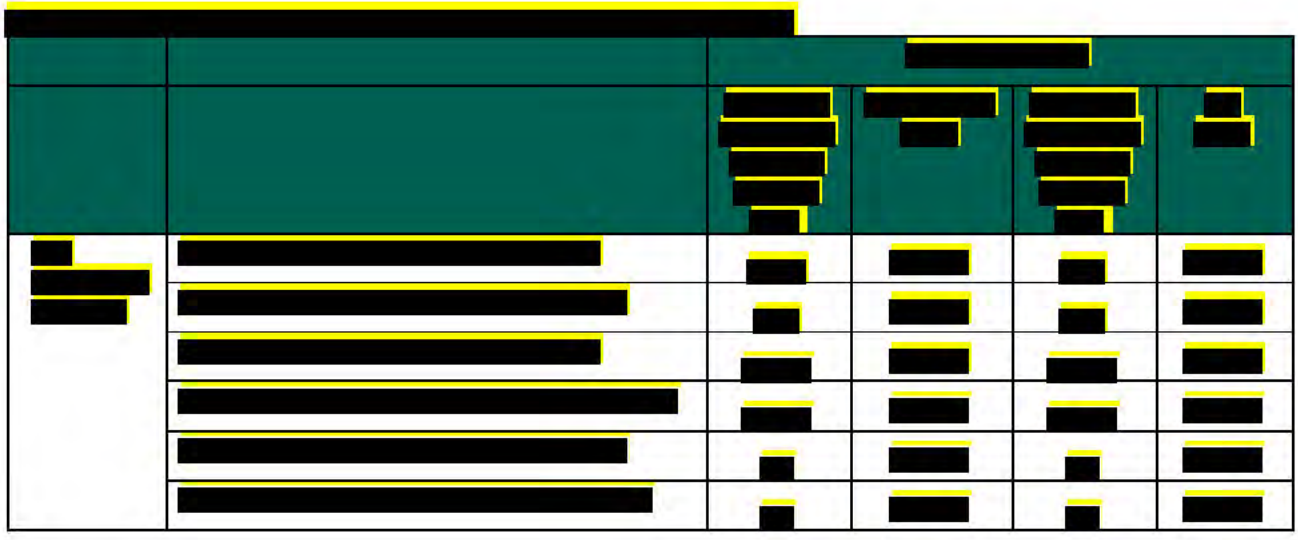
Side effects associated with OCS usage were sourced from a historical cohort study commissioned by AstraZeneca using the Optimum Patient Care Research Database (OPCRD) and the Clinical Practice Research Datalink (CPRD) database to measure the prevalence/incidence of [redacted]

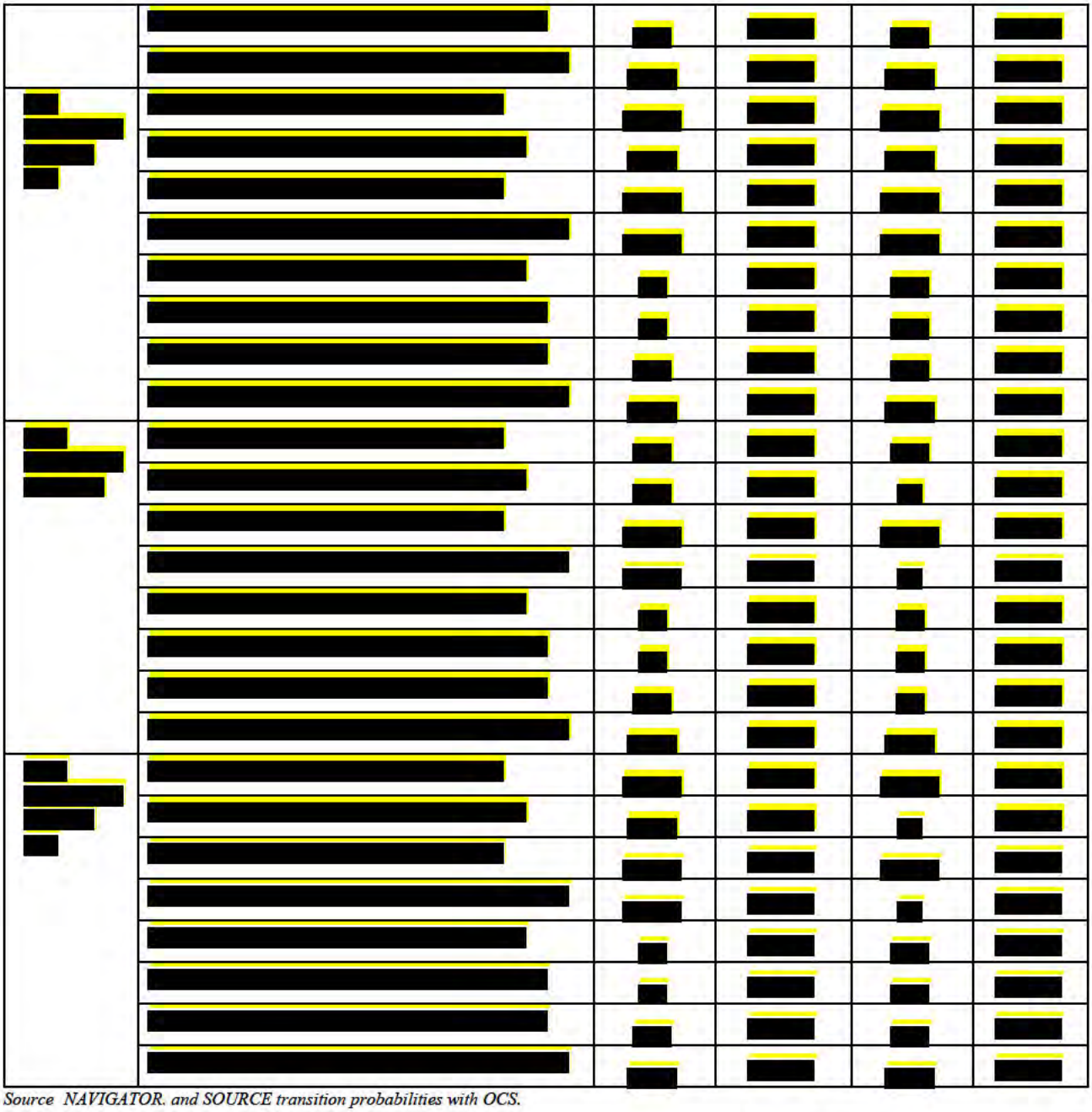


Transition probabilities

Transition probabilities allow for the clinical efficacy data from to be incorporated into the model. In brief, for the 5-state model the probabilities comprise of the likelihood of moving from controlled to uncontrolled state, the likelihood of an exacerbation from either asthma states, and mortality. The mortality probabilities are explained in section 8.3.1. Transition probabilities for tezepelumab and SoC are informed directly from the clinical trials (NAVIGATOR + SOURCE).

The transition probabilities used in the model were calculated by converting the annual rates of exacerbations and mortality into the probability that a patient will experience an exacerbation or mortality within the defined cycle time (set to 4 weeks by default) of the Markov model. These transition probabilities used in the cost-effectiveness model were extracted specifically for the subpopulation with type 2 low asthma. The transition probabilities are calculated from the number of movements from the health state to the other health state divided by the number of times in the health state for each of the transition probabilities. The transition probabilities used in the health economic model are shown in Table 52.





Source NAVIGATOR. and SOURCE transition probabilities with OCS.

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

8.1.2.1 Patient population

The patient characteristics applied in the cost-effectiveness analyses are presented in Table 48. Estimates applied in the health economic modelThese characteristics are sourced from pivotal study NAVIGATOR (ref). According to DSAR (2021), patients that start with biological treatment are characterized by (the average patient)(43):

• 54 years (45-64)

- Asthma debut at 30 years old (15-48)
- Just as often men as women (51/49%)

8.1.2.2 Intervention

Table 51 Intervention.

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	Tezepelumab 210mg every fourth week (16).	Tezepelumab 210mg every fourth week (16).	Tezepelumab 210mg every fourth week (16).
Length of treatment (time on treatment) (mean/median)	Throughout the study period (16).	Mean treatment time was approx. 9.5 years	This is not currently known since biologic treatment was introduced quite recently. Why, patients in the model can be treated throughout their lifetime.
Criteria for discontinuation	Study-specific withdrawal criteria included: anaphylactic reaction to treatment requiring administration of epinephrine, helminth parasitic infestation requiring hospitalization, an asthma-related event requiring intubation, liver function abnormality, or any malignancy.	No reduction of AAER and/or OCS maintenance use.	According to DLS, an assessment is made by the treating physician on the effect on number of exacerbations, but also other measures as asthma control and lung function (93).
The pharmaceutical's position in Danish clinical practice	GINA step 4 and 5.	High-dose ICS treatment (GINA step 5).	Clinical practice follows the DMC guidelines. tezepelumab is expected to be added to the DMC guidelines.

8.1.2.3 Comparators

Table 52 Comparator.

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Posology	PATHWAY: medium-to-high dose ICS+LABA (± other controller medications) NAVIGATOR: medium-to-high dose ICS + ≥1 other controller medication	High-dose ICS+LABA Dupilumab	High-dose ICS+LABA (± other controller medications).

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
	SOURCE: High-dose ICS+LABA + OCS (to be tapered down) ± other controller medications		Dupilumab, and other equal biologics.
Length of treatment	Throughout the study period (16).	Mean treatment time was approx. 28.6 years.	This is not currently known since biologic treatment was introduced quite recently. Why, patients in the model can be treated throughout their lifetime.
The comparator's position in the Danish clinical practice	GINA step 4 and 5.	High-dose ICS treatment (GINA step 5).	Clinical practice follows the GINA, recommended treatment in GINA step 4 and 5.

8.2 Documentation of efficacy outcomes

Table 53. Summary of text regarding *value*.

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Primary endpoint in the study (endpoint's name)	Annualized rate of asthma exacerbations over a period of 52 weeks.	Annualized rate of asthma exacerbations over a period of 52 weeks.
Secondary endpoint (endpoint's name)	Forced expiratory volume in 1 second (FEV1) Asthma Control Questionnaire–6 Asthma Quality of Life Questionnaire Asthma Symptom Diary	Asthma Control Questionnaire–6

Table 54 Summary of text regarding *relevance*.

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Primary endpoint in the study (endpoint's name)	Annualized rate of asthma exacerbations over a period of 52 weeks.	Reduction of exacerbation is a relevant outcome in Danish clinical practice.	Relevant measurement according to guidelines. Asthma exacerbations are used as a measure in clinical practice.

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Secondary endpoint (endpoint's name)	Forced expiratory volume in 1 second (FEV1) Asthma Control Questionnaire–6 Asthma Quality of Life Questionnaire Asthma Symptom Diary		

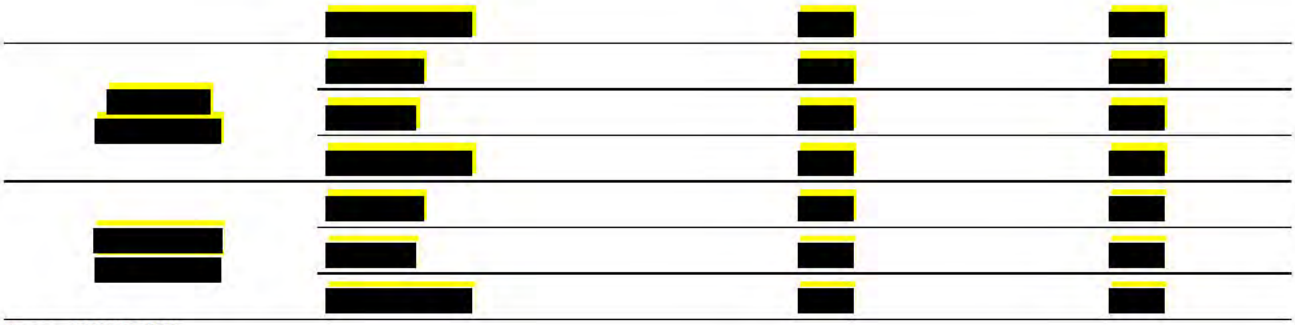
8.2.1 Exacerbation distribution

In the AstraZeneca cost-effectiveness model, only severe exacerbations are considered in the model, while moderate exacerbations are not considered in the model. Moderate exacerbations can be defined as patients experiencing a worsening of their asthma which requires a temporary increase in their ICS dose. According to feedback from clinical experts in advisory boards run by AstraZeneca, moderate exacerbations would be considered clinically equivalent to the health state Uncontrolled Asthma. Thus, by including a health state with Moderate Exacerbations would double count the consequence on the patient's HRQoL and costs from moderate exacerbations since these consequences are already considered in the health state Uncontrolled Asthma.

There are three types of severe exacerbation incorporated in the model: OCS burst (minimum of 3 days OCS use), emergency room or A&E visit, or hospitalization. For each intervention, a distribution of severe exacerbation type is applied to the proportion of the patient cohort that enters the exacerbation state (Table [redacted] 55). This determines the number of patients in each cycle within the exacerbation state that experiences each type of exacerbation in order to determine their HRQoL and costs.

The severe exacerbation distributions for tezepelumab and SoC are informed directly from the NAVIGATOR trials. Severe exacerbations may occur in either controlled or uncontrolled asthma. In the model, exacerbation distributions are stratified by OCS use (i.e. with or without OCS).

Table [redacted]

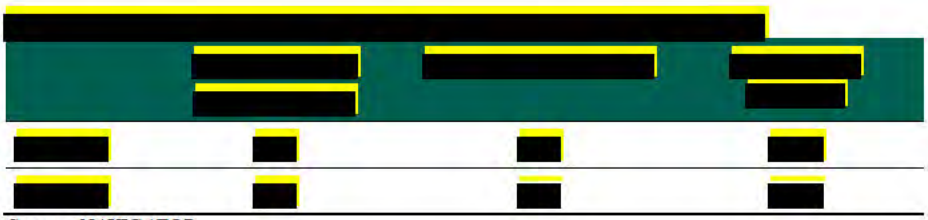


Source: NAVIGATOR.

In both NICE's (NICE TA751) and TLV's (TLV 1733/2019) assessments of dupilumab, it is assumed that after the RCT period there is an increased probability of severe exacerbations both for patients on biologic therapy and SoC. One argument for this assumption is that patients in RCTs may have better outcomes than patients in routine practice due to regular specialist follow-up, optimized care, and improved adherence. Thus, the long-term outcome of exacerbation events cannot be generalized from the short-term outcomes of exacerbation events from the RCT.

On the basis of this argument, AstraZeneca has included an exacerbation multiplier in the health economic model after week 52. The exacerbation multiplier is based on the difference between the AAER during 12 months before the patients were enrolled in NAVIGATOR and the AAER during the 12 months that the patients were enrolled in NAVIGATOR ( ).

The exacerbation multiplier of severe exacerbation only affects the transition from the Controlled and Uncontrolled health states, i.e. it does not alter the probability of patients remaining the in the exacerbation state.



Source NAVIGATOR.

8.2.2 Treatment discontinuation

The cost-effectiveness model considers two types of treatment stopping:

- Natural discontinuation which refers to natural treatment discontinuation during the trial period due to other reasons than treatment effects (lost to follow-up, other health conditions, severe events, etc.)
- Response assessment which refers to treatment stopping due to a lack of response during the assessment week (summarized in Table 48. Estimates applied in the health economic model). The definition of a responder is: 1) a minimum of 5mg dose reduction of OCS, or, 2) Any reduction in AAER.

The treatment discontinuation was applied in the health economic model based on probability data from the pivotal study NAVIGATOR (16). The probability input was applied per cycle as a cyclical probability throughout the model time horizon.

The assessment week in the model is a single timepoint where clinicians determine whether patients should continue using a biologic based on their response to treatment prior to the response week. This response week was set to week 52. It should be noted, patients cannot discontinue from SoC, therefore the treatment-stopping parameters are not applied to SoC.

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

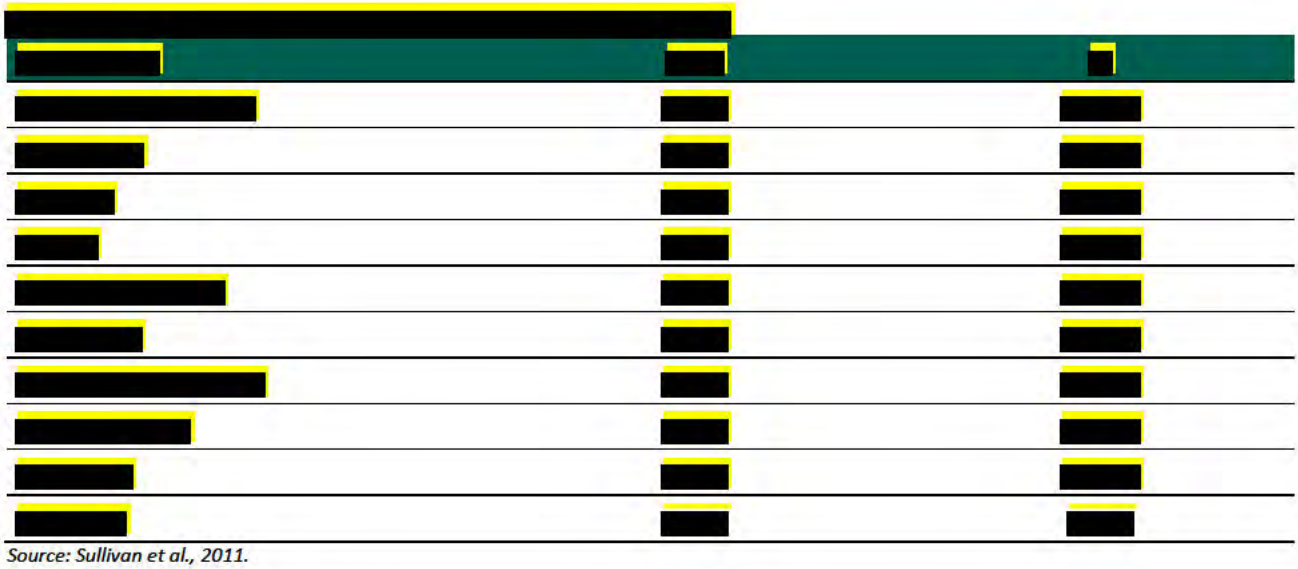
NAVIGATOR and SOURCE Phase III trials administered the European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) questionnaire every two weeks from randomization for up to 52 weeks. In NAVIGATOR, 1059 patients were included, and after the cleaning of the EQ-5D data, 1055 patients had correct EQ-5D responses. In SOURCE, 150 patients were included, and after the cleaning of the EQ-5D data, 148 patients had correct EQ-5D responses.

Both NAVIGATOR and SOURCE reference the mapping function developed by Jensen et al (94) in order to use the preference weights based on the general Danish population. Utility values from NAVIGATOR and SOURCE were used for the health states "Controlled asthma" and "Uncontrolled asthma". The utility decrement associated with each type of exacerbation (OCS burst, A&E visit, and hospital admission) was assumed to be the same in all treatment arms. This assumption is consistent with established economic models of biologic treatments for asthma (95-98). Utility decrement values for OCS burst, A&E visit, and hospital admission were sourced from Lloyd *et al.* (92) (Table 48). The Lloyd study prospectively measured EQ-5D-3L values over a 4-week period for 112 patients with severe asthma, and observed a disutility associated with exacerbations by measuring the difference in EQ-5D-3L between patients without an exacerbation (85 patients) and with exacerbation without hospitalisation (22 patients), and with asthma-related hospitalisation (5 patients). For modelling purposes, disutility associated with an exacerbation leading to an ER visit was conservatively assumed to be the same as that for an OCS burst (92). Due to that the utility decrements were based on a published study, and that AstraZeneca does not have access to the raw data, it was not possible to map the EQ-5D-3L data published by Lloyd et al. (92) into EQ-5D-5L data, nor was it possible to use the preference weights based on the general Danish population. The data in the Lloyd et al. (92) publication was collected within the INNOVATE trial {Humbert, 2005 #191}, and the utility data were first used in the cost-effectiveness study of Tiotropium published by Willson et al {Willson, 2014 #266}. Analyses from the NAVIGATOR trial showed that the utility weights for the [redacted]. Thus, one could assume that if the utility decrements by Lloyd et al were mapped into EQ-5D-5L, the utility decrement would be even greater. Thus, the utility decrement used in the Tezepelumab cost-effectiveness analysis could be seen as an underestimation, and a conservative approach. However, the rational for using the utility decrements published by Lloyd et al. (92) is due to that several assessments of biologic treatments for patients with severe uncontrolled asthma: the TLV assessments of Dupixent (1733/2019) (99), and Cinqaero (666/2016) (100), the NoMA assessments of Nucala (18/02297) (101), and Cinqaero (2017-04051) (102), as well as the NICE assessments of Dupixent (TA 751) (103), and Fasenra (TA 565) (104). By using the same utility decrements as the previous assessments enable the methodology used in the cost-effectiveness analysis to be more comparable and consistent with the decision made by other payer authorities.

An age-specific utility weighting was applied to the trial data to adjust for patients' mean age when entering the model, and when the age of the model cohort increases with time. Age adjustment aims to reflect the monthly HRQoL of life of living with severe asthma for patients undergoing treatment according to their responses. Age-specific utilities for the monthly utilities for tezepelumab was adjusted according to the DMC guidelines (105).

OCS-related adverse event disutility

A fixed disutility value is applied for each OCS-related adverse event (Table 57 Base case disutility values by OCS-related adverse event. EQ-5D-3L data is used within the model based on published data (106). Values are input as annual disutility, which are then converted to cyclical values to be applied.



Source: Sullivan et al., 2011.

8.3.1 Mortality

Mortality is captured within the cost-effectiveness model as all-cause mortality and exacerbation specific mortality.

All-cause mortality

The risk of all-cause mortality was estimated using Danish national life-tables from 2021 (87), making it possible to apply age- and sex-specific mortality risks to all health states in the model. Asthma-related mortality was not subtracted from all-cause mortality as the impact of the relatively small number of asthma deaths was considered unlikely to impact the results (and would not impact incremental differences in mortality in any case) i.e. all patients in all health states experience all-cause mortality, and both all-cause and asthma-related mortality are applied together in the exacerbation states.

Exacerbation specific mortality

Asthma-related deaths from the severe exacerbation states were calculated using data from Roberts et al., 2013 (107), Watson et al., 2007 (108), and data from a National Review for Asthma Deaths (NRAD), 2017 (109) and shown in Table 58 Mortality risk by severe exacerbation management strategy (transition probabilities per cycle).

This approach was optimised to reflect both the mortality attributable to asthma hospitalisation and the inherent variation in this risk across the most granular stratification of age categories available.

This approach included the assumption that asthma-related mortality can only occur from the exacerbation state at specific asthma-related mortality rates. For exacerbations requiring a hospital admission, the cost-effectiveness model

uses mortality data from Watson *et al* (108), combined with Roberts *et al* (107), and for exacerbations not requiring a hospital admission (i.e. OCS burst and A&E visits) from Watson *et al* (108), combined with locations from the NRAD (Royal college of physicians 2017) (109).

Source: Roberts *et al.* 2013, Watson *et al.* 2007, and data from a National Review for Asthma Deaths (NRAD) (Royal college of physicians 2017).

8.4 Resource use and costs

Treatment costs

Treatment costs are applied in the model as the drug acquisition cost (Table 61) and administration cost (Table 60. Drug administration costs. Drug acquisition cost was applied in the model based on frequency of doses. The frequency of biologic treatment with tezepelumab is one dose of 210 mg per every four weeks.

The drug administration cost was applied in the model based on the mepolizumab assessment with a split between home administration (70%) and hospital administration (30%) (18). In the cost-effectiveness analyses, both the patient time cost, i.e. DKK 173.71 per dose, and the hospital administration cost, i.e. DKK 251.77 per dose, were included in analyses.

The treatment cost for SoC is equal to high-dose ICS and LABA. Bufomix is the most commonly used therapy in Denmark, thus, AstraZeneca uses Bufomix as the comparator. The AIP price for Bufomix 360 doses per pack is DKK 797.65. High-dose Bufomix equals 120 doses per month.

For the OCS, Prednisolon (Orifarm Healthcare) was used. The AIP price for Prednisolon 100 tablets á 5 mg is DKK 68.55.

Table 59. Drug acquisition costs.

Intervention	DKK	Product
Tezepelumab (cost every four weeks)	8 890.90 (expected AIP)	210 mg
High-dose ICS+LABA (cost per month)	265.88	Bufomix (high-dose, i.e. two doses twice a day)

OCS (cost per mg)	0.14	Prednisolon (100 tablets, a 5 mg)

Source www.medicinpriser.dk

Table 60. Drug administration costs.

Intervention	Units	Unit costs (DKK)	Total costs (DKK)
Nurse time (drug administration)	495	9.3	4 603.1
Patient time (treatment)	570.7	3.0	1 712.1
Patient time (travel)	847.9	3.0	2 543.7
Medical equipment (hospital)	14.1	100.0	1 413.1
Facilities (hospital)	570.7	0.3	152.2
Total administration cost for 1 and 2 years of treatment			10 438.4
Total administration cost per year			5 219.2
Total administration cost per dose			**426.06**
Whereof patient time			173.71
Whereof hospital administration			251.77

Source mepolizumab assessment (18).

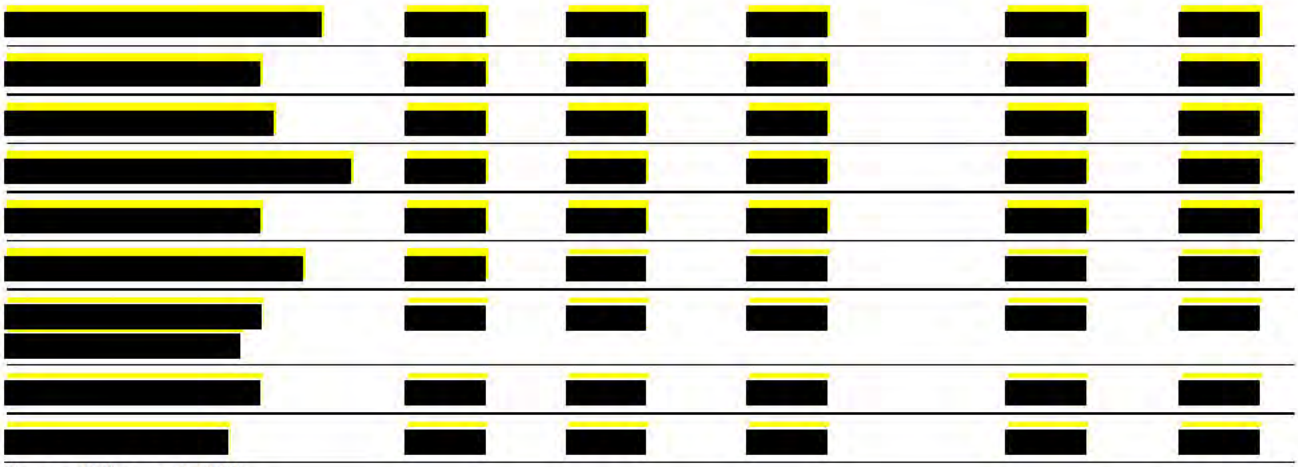
Disease management costs

Disease management costs are based on healthcare health state occupancy, with different costs for the three exacerbation states. These costs are a function of healthcare resource use, based on the expected frequency of resource use for patients in each health state (Table 61[redacted]. and their associated unit costs Table 62 Healthcare resource utilitzation unit costs (DKK). Resource use frequency values are sourced from Willson et al., (110).

When a patient experiences an exacerbation event the following assumptions are applied for costs:

- An OCS burst will incur the healthcare resource utilization and associated costs of an exacerbation without hospitalization for the duration of that exacerbation
- An A&E visit will incur the healthcare resource utilization and associated costs of an exacerbation without hospitalization for the duration of that exacerbation as well as a one-off cost of an A&E visit
- Hospitalization exacerbation will incur the healthcare resource utilization and associated costs of an exacerbation with hospitalization for the duration of that exacerbation as well as a one-off cost for hospitalization.

[redacted]



Source Willson et al. (110).

Table 62 Healthcare resource utilitzation unit costs (DKK).

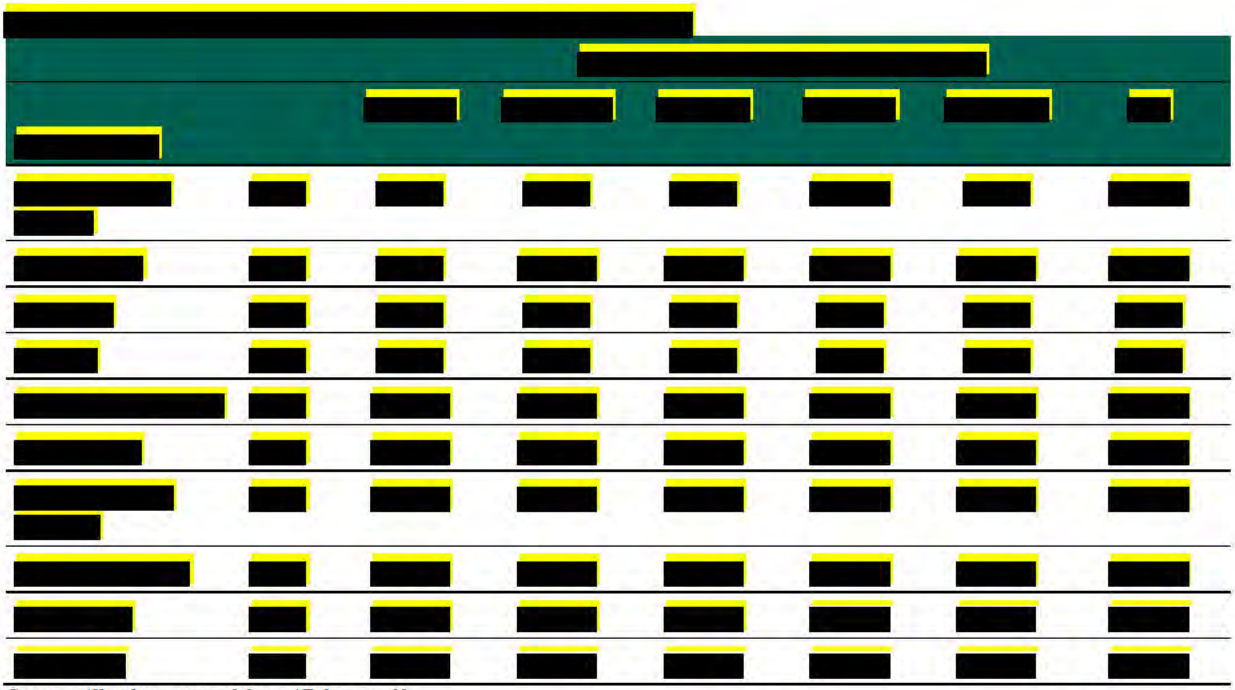
Parameter	Unit cost (DKK)	Source
GP Visit (Outpatient)	148.35 kr	https://www.laeger.dk/sites/default/files/honorartabel_2019_oktober-1.pdf
GP Visit (Home)	791.16 kr	https://www.laeger.dk/sites/default/files/honorartabel_2019_oktober-1.pdf
Nurse Visit (Outpatient)	550.00 kr	https://medicinraadet.dk/media/weslftgk/vaerdisaetning-af-enhedsomkostninger-vers-13_adlegacy.pdf
Nurse Visit (Home)	550.00 kr	https://medicinraadet.dk/media/weslftgk/vaerdisaetning-af-enhedsomkostninger-vers-13_adlegacy.pdf
Respiratory Specialist Visit (Outpatient)	2 180.00 kr	https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2022 (DRG 04MA98)
Transportation to hospital	231.39 kr	mepolizumab assessment in Amgros/Medicinrådet "Udvidet sammenligningsgrundlag" (18).
Spirometry	124.26 kr	https://medicinraadet.dk/media/weslftgk/vaerdisaetning-af-enhedsomkostninger-vers-13_adlegacy.pdf
Administration cost per dose	194.65 kr	mepolizumab assessment in Amgros/Medicinrådet "Udvidet sammenligningsgrundlag" (18).
A&E Visit	2 180.00 kr	https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2022 (DRG 04MA98)
Hospitalisation	23 486.00 kr	https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2022 (DRG 04MA20)

**Home visits assumes to have the same unit costs as visits in the primary care.*

OCS-related adverse event costs

In addition to the costs of exacerbations, costs are applied within the model for treatment of OCS-related adverse events (Table 65). Costs of OCS adverse events were sourced from the same study as OCS adverse event frequency (a historical cohort study commissioned by AstraZeneca using the Optimum Patient Care Research Database (OPCRD)

and the Clinical Practice Research Datalink (CPRD) database). Although this was a UK study, the same costs were applied for Denmark (after conversion into DKK). The OCS-related adverse event costs were imputed as cyclical costs for the patient cohort on maintenance OCS use at baseline for the proportion of patients experiencing the adverse events.



Source All values sourced from AZ data on file

Patients costs

Are included in the administration costs and based on the calculations originally made by DMC/Amgros (18).

8.5 Results

8.5.1 Cost-minimization analysis for the subgroup with type 2 asthma

The results from the CMA with tezepelumab compared to dupilumab are shown in Table 66. Dupilumab have higher dosing interval compared to Tezepelumab, and a loading dose the first year.

Table 64 Result from the CMA comparing tezepelumab with dupilumab.

	Tezepelumab (DKK)	Dupilumab (DKK)	Differencel (DKK)
Drug acquisition costs	905 483	1 007 906	-102 423
Health care costs	406 259	478 408	-72 149
Patient costs	24 188	26 387	-2 199

	Tezepelumab (DKK)	Dupilumab (DKK)	Differencel (DKK)
Total costs	1 335 929	1 486 314	**-150 385**

8.5.2 Base case overview of the cost-utility analyses

Table 65 Base case overview.

Comparator	Standard of care
Type of model	Markov model
Time horizon	60 years (life time)
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in NAVIGATOR (ref) and SOURCE (ref). Danish population weights were used to estimate health-state utility values.
Included costs	Pharmaceutical costs Hospital costs Costs of adverse events Patient costs
Dosage of pharmaceutical	210 mg per dose, every 4th week.
Average time on treatment	Intervention: 9-10 years SoC: 27-28 years

8.5.3 Base case results from the cost-utility analyses

The base case result for the type 2 low asthma subpopulation is presented in Table 66 Base case results. This population was on high-dose ICS without maintenance OCS use.

The ICERs presented in this section is based on the AIP for tezepelumab. However, AstraZeneca will give a rebate that are competitive with the other reimbursed/recommended biologics.

Table 66 Base case results from the CUA.

	Type 2 low asthma		
Per patient	**tezepelumab**	**SoC**	**Difference**
Life years gained			
Total life years gained	15.336	14.780	0.557

QALYs			
Total QALYs	11.948	11.474	0.474
Costs			
Total costs	1 314 664	603 367	711 297
Drug costs	843 510	51 329	792 181
Healthcare costs	452 128	531 540	-79 413
Patients costs	19 026	20 498	-1 472

Incremental results	tezepelumab vs. SoC
ICER (per QALY)	1 499 808

8.6 Sensitivity analyses

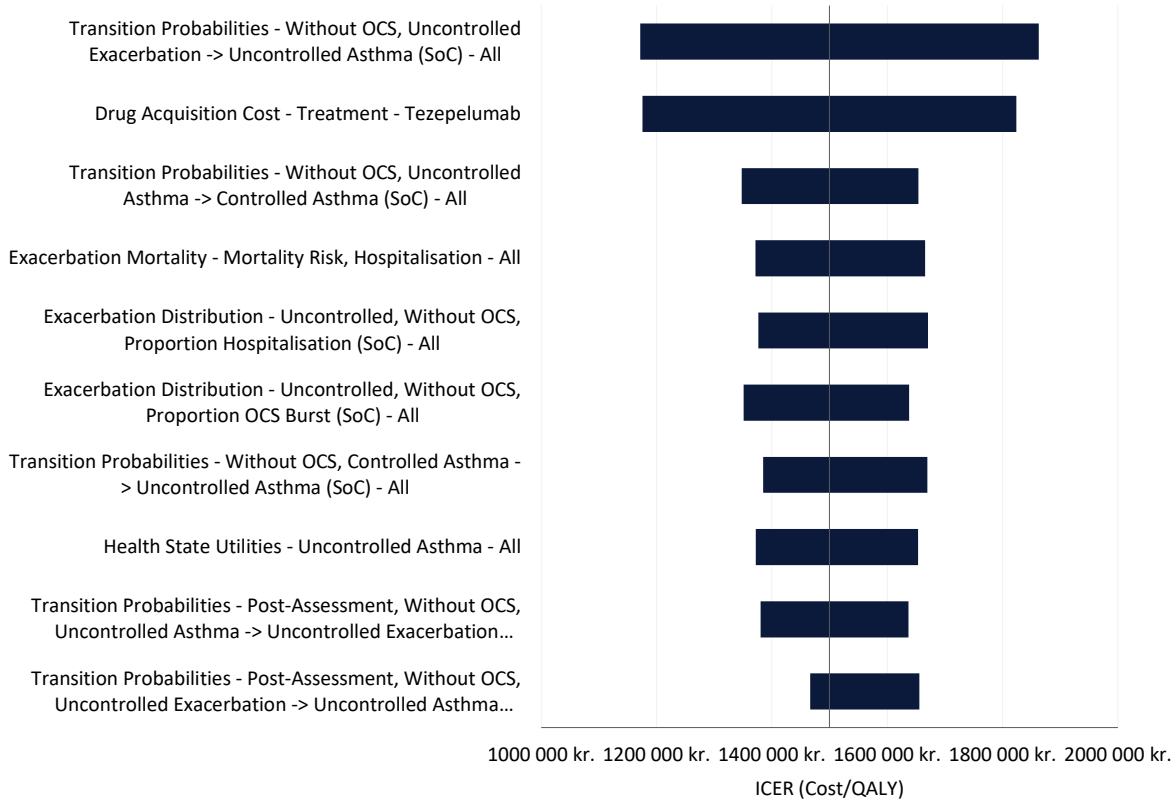
8.6.1 Deterministic sensitivity analyses

The Deterministic Sensitivity Analysis section consists of two parts:
1) The built-in Deterministic Sensitivity Analysis from the cost-effectiveness model
2) Additional Deterministic Sensitivity Analysis

The built-in Deterministic Sensitivity Analysis from the cost-effectiveness model

The built-in Deterministic Sensitivity Analysis from the cost-effectiveness model is presented as a Tornado diagram for the T2 low population. The built-in Deterministic Sensitivity analysis shows the 10 parameters that have the largest impact on the base case ICER.

Figure 10 Tornado diagram for type 2 low asthma.



Additional Deterministic Sensitivity Analysis

In the additional Deterministic Sensitivity Analysis presented in Table 67 Scenario analyses. following inputs were tested:

- Time-horizon
- HSUV decrements
- Exacerbation multiplier
- Hospitalization cost
- Restrictions of exacerbations
- Discount rates for costs and benefits changed simultaneously

Time-horizon
In this scenario, the time-horizon in the model were varied with 40, 30 and 20 years, respectively.

Exacerbation multiplier
In this scenario, the exacerbation multiplier was excluded.

Hospitalization costs
The hospitalization costs for the exacerbations was varied with +/-20%.

Restrictions of exacerbations
Exacerbation events are one of the main driver for the costs and health outcomes in the model. Thus, in this scenario, the type 2 low asthma population are restricted with 3 and more, and 4 and more exacerbations. However, the scenario with restriction of 4 and more exacerbation should be interpreted with caution since the number of patients in the pivotal study with type 2 asthma with 4 or more exacerbation is 3% of the total high-dose ICS study population.

Discont rates for costs and benefits changed simultaneously
In this scenario, the discount rates for costs and benefits were changed simultaneously with 0% and 6%.

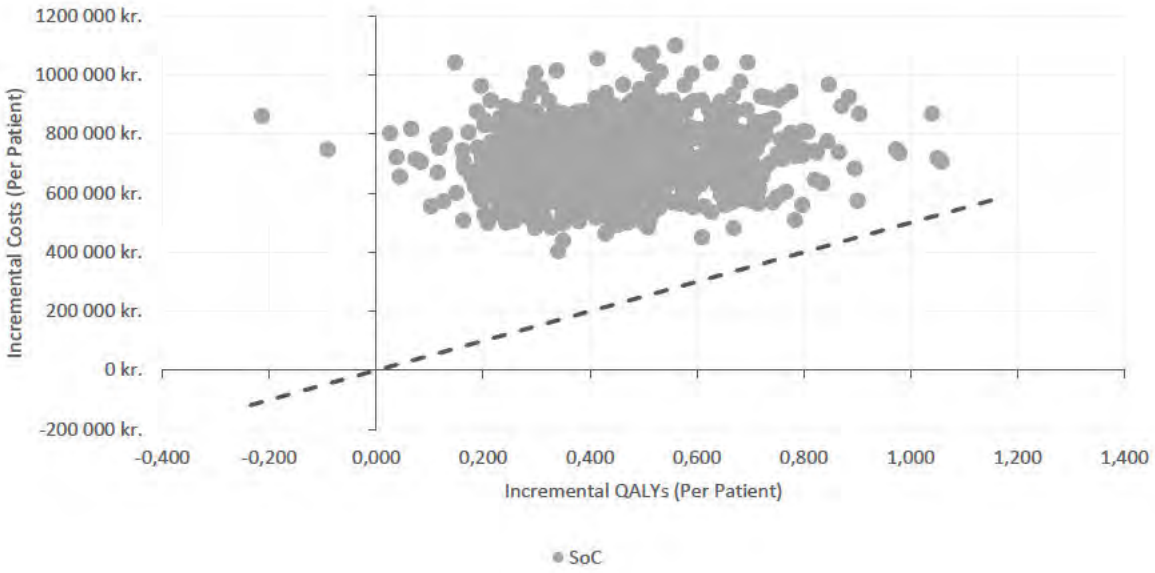
Table 67 Scenario analyses.

Parameters		Incremental costs	Incremental QALYs	ICER (DKK/QALYs)
Base case ICER		711 297	0.474	1 499 808
Time horizon (60 years)	40 years	710 978	0.472	1 507 609
	30 years	704 312	0.431	1 634 871
	20 years	668 572	0.305	2 189 249
Exacerbation multiplier	Not included	738 716	0.359	2 059 483
Hospitalization costs	+20%	703 405	0.474	1 483 166
	-20%	719 189	0.474	1 516 449
Restriction of exacerbations	3 or more	599 402	0.912	657 526
	4 or more	357 493	2.025	176 574
Discount rates for costs and benefits changed simultaneously	0%	932 528	0.849	1 097 984
	6%	607 953	0.334	1 821 069

8.6.2 Probabilistic sensitivity analyses

Probabilistic sensitivity analyses (PSA) were conducted to establish the impact of parameter uncertainty of the cost-effectiveness of tezepelumab compared to SoC. A total of 1,000 iterations were run. For parameters with no information on the actual standard error (SE), the SE was set to a 10% variance. An overview of all assumptions regarding the PSA is presented in Appendix J.
Figure 11 presents the cost-effectiveness plane, which showed that majority of all 1,000 iterations were in the North-East quadrant indicating that tezepelumab is more effective and more costly in comparison to SoC in all iterations.

Figure 11 Cost-effectiveness plane for the type 2 low asthma population.



9. Budget impact analysis

The budget impact calculations are based on AIP at list prices, and the same health state costs used in the cost-effectiveness model. These costs are for the health states "Uncontrolled asthma", "Controlled asthma", "OCS burst", "A&E visit", and "Hospitalization". The costs in these health states are considered as healthcare costs in the budget impact analysis, and the patients transportation cost is note included in the calculation.

As shown in Table 76 Expected budget impact of recommending the pharmaceutical for the current indication, an introduction of Tezspire will lead to an increased budget impact, mainly drived by the drug acquisition costs. The health care expenditure will be reduces by an introduction of Tezspire, mainly driven by that treatment with Tezspire leads to reduced number of exacerbations.

To have the budget impact analyses interlinked with the cost-effectiveness model, the budget impact model (BIM) is plugged-in to the cost-effectiveness model. The BIM is separated into two parts. One BIM is interlinked with the cost-effectiveness model for the two subpopulations in the cost-utility analyses, the population with High FeNo and the population with type 2 low asthma and with 2, 3 and 4+ AAER. Thus, when changes are made to the subpopulation parameters, the interlinked BIM are automatically updated. This BIM can be found on the sheet called "BIM from CUA". The other BIM is covering the two subpopulations within the CMA, population with type 2 high asthma and the allergic asthma population. This BIM can be found on the sheet called "BIM from CMA". The budget impact analyses includes only undiscounted hospital costs, administration costs and drug acquisition costs. The budget impact analyses does not consider any discontinuation of biologic treatments.

Number of patients

For details regarding the number of patients expected to be treated in the BIM see section 5.

Table 68 Number of patients expected to be treated over the next five-year period - if the pharmaceutical is introduced.

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	2022	2023	2024	2025	2026
Number of new patients in Denmark who are expected to use the pharmaceutical in the coming years	0	62	62	62	62
T2 high (EOS ≥150 AND/OR) adult patients and adolescents ≥12 years	0	21	21	21	21
Allergic adult patients and adolescents ≥12 years	0	9	9	9	9
T2 low adult patients and adolescents ≥12 years	0	32	32	32	32
Total number of patients (accumulative)	0	62	124	186	248

It is not expected that tezepelumab will be used in Denmark, if it is not recommended by the DMC.

Table 69 Number of patients expected to be treated over the next five-year period - if the pharmaceutical is NOT introduced.

	Year 1 2022	Year 2 2023	Year 3 2024	Year 4 2025	Year 5 2026
Number of new patients in Denmark who are expected to use the pharmaceutical in the coming years	0	0	0	0	0
T2 high (EOS ≥150 with or without high FeNO) adult patients and adolescents ≥12 years	0	0	0	0	0
Allergic adult patients and adolescents ≥12 years	0	0	0	0	0
T2 low with 3+ AAER adult patients and adolescents ≥12 years	0	0	0	0	0
FeNO only adult patients and adolescents ≥12 years	0	0	0	0	0
Total number of patients (accumulative)	0	0	0	0	0

Expenditure per patient

Table 70 Costs per patient per year for the subpopulation with type 2 asthma - if the pharmaceutical is recommended.

	Year 1 2022	Year 2 2023	Year 3 2024	Year 4 2025	Year 5 2026
Patient population	0	21	21	21	21
Proportion Tezepelumab	50%	50%	50%	50%	50%
Proportion Dupilumab	50%	50%	50%	50%	50%

Drug aqusition costs Tezepelumab	0 kr	1 213 608 kr	1 213 608 kr	1 213 608 kr	1 213 608 kr
Drug aqusition costs Dupilumab	0 kr	1 260 285 kr	1 260 285 kr	1 260 285 kr	1 260 285 kr
Administration Tezepelumab	0 kr	26 570 kr	26 570 kr	26 570 kr	26 570 kr
Administration Dupilumab	0 kr	55 184 kr	55 184 kr	55 184 kr	55 184 kr
Total cost	**0 kr**	**2 555 647 kr**	**2 555 647 kr**	**2 555 647 kr**	**2 555 647 kr**
Total cost per patient	**0 kr**	**121 697 kr**	**121 697 kr**	**121 697 kr**	**121 697 kr**

Table 71 Costs per patient per year for the subpopulation with allergic asthma - if the pharmaceutical is recommended

	Year 1 2022	Year 2 2023	Year 3 2024	Year 4 2025	Year 5 2026
Patient population	0	9	9	9	9
Proportion Tezepelumab	50%	50%	50%	50%	50%
Proportion Dupilumab	50%	50%	50%	50%	50%
Drug aqusition costs Tezepelumab	0 kr	520 118 kr	520 118 kr	520 118 kr	520 118 kr
Drug aqusition costs Dupilumab	0 kr	540 122 kr	540 122 kr	540 122 kr	540 122 kr
Administration Tezepelumab	0 kr	11 387 kr	11 387 kr	11 387 kr	11 387 kr
Administration Dupilumab	0 kr	23 650 kr	23 650 kr	23 650 kr	23 650 kr
Total cost	**0 kr**	**1 095 277 kr**	**1 095 277 kr**	**1 095 277 kr**	**1 095 277 kr**
Total cost per patient	**0 kr**	**121 697 kr**	**121 697 kr**	**121 697 kr**	**121 697 kr**

Table 72 Costs per patient per year for the subpopulation with type 2 low asthma - if the pharmaceutical is recommended (100% on Tezepelumab)..

	Year 1 2022	Year 2 2023	Year 3 2024	Year 4 2025	Year 5 2026
Patient population	0	32	32	32	32
Drug aqusition costs	0 kr	3 635 266 kr	3 017 493 kr	2 743 054 kr	2 493 949 kr
Controlled asthma	0 kr	35 290 kr	46 533 kr	45 942 kr	45 142 kr
Uncontrolled asthma	0 kr	356 120 kr	299 231 kr	290 647 kr	287 588 kr
OCS burst	0 kr	162 112 kr	168 562 kr	176 191 kr	182 092 kr

A&E visit	0 kr	12 462 kr	12 365 kr	12 784 kr	13 107 kr
Hospitalization	0 kr	129 005 kr	195 082 kr	226 617 kr	251 056 kr
OCS use	0 kr	2 463 kr	1 853 kr	1 831 kr	1 807 kr
Adverse events	0 kr	40 667 kr	21 214 kr	20 070 kr	19 070 kr
Total cost	**0 kr**	**4 330 255 kr**	**3 739 265 kr**	**3 495 236 kr**	**3 272 935 kr**
Total cost per patient	**0 kr**	**135 320 kr**	**116 852 kr**	**109 226 kr**	**102 279 kr**

Table 73 Costs per patient per year for the subpopulation with type 2 asthma - if the pharmaceutical is NOT recommended.

Cost per patient	Year 1 2022	Year 2 2023	Year 3 2024	Year 4 2025	Year 5 2026
Patient population	0	21	21	21	21
Proportion Tezepelumab	0%	0%	0%	0%	0%
Proportion Dupilumab	100%	100%	100%	100%	100%
Drug aqusition costs Tezepelumab	0 kr	0 kr	0 kr	0 kr	0 kr
Drug aqusition costs Dupilumab	0 kr	2 520 570 kr	2 520 570 kr	2 520 570 kr	2 520 570 kr
Administration Tezepelumab	0 kr	0 kr	0 kr	0 kr	0 kr
Administration Dupilumab	0 kr	110 368 kr	110 368 kr	110 368 kr	110 368 kr
Total cost	**0 kr**	**2 630 938 kr**	**2 630 938 kr**	**2 630 938 kr**	**2 630 938 kr**
Total cost per patient	**0 kr**	**125 283 kr**	**125 283 kr**	**125 283 kr**	**125 283 kr**

Table 74. Costs per patient per year for the subpopulation with allergic asthma - if the pharmaceutical is NOT recommended

	Year 1 2022	Year 2 2023	Year 3 2024	Year 4 2025	Year 5 2026
Patient population	0	9	9	9	9
Proportion Tezepelumab	0%	0%	0%	0%	0%
Proportion Dupilumab	100%	100%	100%	100%	100%
Drug aqusition costs Tezepelumab	0 kr	0 kr	0 kr	0 kr	0 kr
Drug aqusition costs Dupilumab	0 kr	1 080 244 kr	1 080 244 kr	1 080 244 kr	1 080 244 kr
Administration Tezepelumab	0 kr	0 kr	0 kr	0 kr	0 kr

Administration Dupilumab	0 kr	47 301 kr	47 301 kr	47 301 kr	47 301 kr
Total cost	**0 kr**	**1 127 545 kr**	**1 127 545 kr**	**1 127 545 kr**	**1 127 545 kr**
Total cost per patient	**0 kr**	**125 283 kr**	**125 283 kr**	**125 283 kr**	**125 283 kr**

Table 75 Costs per patient per year for the subpopulation with type 2 low asthma - if the pharmaceutical is NOT recommended (100% on SoC).

	Year 1 2022	Year 2 2023	Year 3 2024	Year 4 2025	Year 5 2026
Patient population	0	32	32	32	32
Drug aqusition costs	0 kr	144 727 kr	143 482 kr	142 057 kr	140 539 kr
Controlled asthma	0 kr	43 128 kr	55 900 kr	55 567 kr	54 986 kr
Uncontrolled asthma	0 kr	468 015 kr	395 218 kr	362 813 kr	358 879 kr
OCS burst	0 kr	231 179 kr	351 679 kr	357 248 kr	353 439 kr
A&E visit	0 kr	12 456 kr	21 444 kr	21 795 kr	21 560 kr
Hospitalization	0 kr	531 309 kr	677 218 kr	682 534 kr	675 115 kr
OCS use	0 kr	3 239 kr	1 725 kr	1 704 kr	1 682 kr
Adverse events	0 kr	53 468 kr	14 374 kr	14 196 kr	14 009 kr
Total cost	**0 kr**	**1 430 813 kr**	**1 644 943 kr**	**1 622 014 kr**	**1 604 517 kr**
Total cost per patient	**0 kr**	**34 067 kr**	**39 165 kr**	**38 619 kr**	**38 203 kr**

Budget impact

Table 76 Expected budget impact of recommending the pharmaceutical for the current indication

	Year 1 2022	Year 2 2023	Year 3 2024	Year 4 2025	Year 5 2026
T2 high (EOS ≥150 AND/OR FeNO) adult patients and adolescents ≥12 years					
Total cost if the pharmaceutical is recommended	0 kr	2 555 647 kr	5 109 251 kr	7 662 854 kr	10 216 457 kr
Total cost if the pharmaceutical is not recommended	0 kr	2 630 938 kr	5 261 877 kr	7 892 815 kr	10 523 754 kr
Subpopulation total budget impact	**0 kr**	**-75 291 kr**	**-152 626 kr**	**-229 961 kr**	**-307 296 kr**

Allergic adult patients and adolescents ≥12 years					
Total cost if the pharmaceutical is recommended	0 kr	1 095 277 kr	2 189 679 kr	3 284 080 kr	4 378 482 kr
Total cost if the pharmaceutical is not recommended	0 kr	1 127 545 kr	2 253 338 kr	3 379 131 kr	4 504 925 kr
Subpopulation total budget impact	**0 kr**	**-32 268 kr**	**-63 659 kr**	**-95 051 kr**	**-126 443 kr**
T2 low adult with patients and adolescents ≥12 years					
Total cost if the pharmaceutical is recommended	0 kr	4 330 255 kr	8 069 520 kr	11 564 756 kr	14 837 691 kr
Total cost if the pharmaceutical is not recommended	0 kr	1 430 813 kr	3 075 756 kr	4 697 770 kr	6 302 287 kr
Subpopulation total budget impact	**0 kr**	**2 899 442 kr**	**4 993 765 kr**	**6 866 986 kr**	**8 535 404 kr**

10. Discussion on the submitted documentation

Patient population estimations

[redacted]. However, the size of the Type 2 low population with EOS<150 are more uncertain since these patients are not covered by existing biologics. In the NAVIGATOR trial, a total of 15,6% of the severe uncontrolled asthma patients receiving high dose ICS had Type 2 low. [redacted]

ITC (and SLR)

The analyses presented in this report are associated with a number of strengths. The indirect comparisons were based on a recent, comprehensive systematic literature review that identified relevant evidence for tezepelumab and comparator biologics for the treatment of moderate-to-severe asthma. In addition, the SLR was conducted in adherence to best practices provided by PRISMA guidance.84 Searches were conducted across multiple databases by an experienced information specialist, and grey literature searches and hand searches were conducted. Study screening, data abstraction, and quality assessment were performed in duplicate. An SAP for conducting NMAs was used to guide the analyses presented in this report. Statistical analyses were performed according to well-established methods outlined by the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) Technical Support Documents (TSDs). (111) A thorough examination of heterogeneity between trials was conducted, a process that was guided by KEEs to identify the patient and trial characteristics with the potential to bias estimates of comparative efficacy. Subgroup analyses were performed for the purpose of mitigating the effects of heterogeneity, as well as to generative estimates of comparative efficacy in clinically relevant subpopulations. Although all efforts were made to conduct a robust and detailed analysis, limitations should be considered when interpreting the results. NMA-specific assumptions including homogeneity, exchangeability, and consistency were made to derive relative treatment effects between interventions that may not have been compared directly in RCTs. The exchangeability assumption in particular may have been violated in the present analysis given the observed heterogeneity in eligibility criteria and clinically important patient characteristics across included trials, as well as the nuanced differences in target populations for each biologic. Analysis-specific assumptions were also made, such as pooling of non-placebo control arms (i.e., best standard of care [BSC] and optimized asthma treatment [OAT]) with placebo.

Unpublished data

[redacted] (77)

Cost-minimization, cost-effectiveness and budget impact analyses

Cost-minimization analyses including drug acquisition costs and drug administration costs for tezepelumab compared to dupilumab were conducted for the type 2 high asthma and the allergic asthma populations.

The cost-minimization analyses and the budget impact analyses showed a lower annual cost for tezepelumab compared to dupilumab both for the type 2 high asthma and the allergic asthma populations. This cost difference was driven by the drug administration costs due to more frequent dosing interval with dupilumab compared to tezepelumab.

Cost-effectiveness models that utilizes a Markov state-transition framework was adapted to the Danish setting and used to perform the cost-effectiveness analysis where tezepelumab + SoC were compared with SoC for the high FeNO and type 2 low asthma populations. Key model inputs sourced from the tezepelumab trial were efficacy and safety inputs, and utilities. Healthcare resource use and costs were estimated from Danish public sources and published literature. Incremental cost-effectiveness ratios (ICERs) were assessed for life-years (LY) gained and quality-adjusted life years (QALYs) gained.

Further, since there are currently limited data to describe Danish severe asthma patients, this add some uncertainty to the cost-effectiveness analysis results. On the other hand, we do not think this has a substantial impact since we have used several registry sources that we believe is representative also for a Danish setting.

The modelling methodology used, is well established within the asthma field, and is similar to the modelling approach of dupilumab, which was endorsed by NICE. The major difference in the modelling approach is that in the AstraZeneca model, only severe exacerbation were considered to avoid double counting of the moderate exacerbation that are already covered in the Uncontrolled asthma health state avoiding to feedback from clinical experts. The majority of the included data were collected in the NAVIGATOR and SOURCE trials, and therefore directly applicable to the modelled population and decision problem. In general, this is preferred to reduce the uncertainty around the model results, especially for the parameters with high impact on the ICER. The enclosed cost-effectiveness model gives the opportunity to select other parametric functions, so that DMC can check the impact of cost effectiveness for the various parametric functions. The assumed standard treatment modality follows the GINA guidelines and thus also Danish clinical practice.

The cost-effectiveness analyses showed an increased incremental cost and increased incremental utilities for both the high FeNO and type 2 low asthma populations, indicating that tezepelumab + SoC were more effective but more costly compared to SoC alone.

11. List of experts

Danish experts has been consulting AstraZeneca in the process of developing this application to fully understand the Danish clinical practice and to thereby adapt our application accordingly, however no Danish experts has been used as a direct reference in this application.

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

Objective of the literature search: To inform an indirect treatment comparison (ITC) to compare the different biologic treatments in adults with moderate-to-severe uncontrolled asthma.

This SLR was performed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions(1) and reported in alignment with the Preferred Reporting Items for Systematic Literature Reviews and Meta-Analyses (PRISMA) statement.(2, 3) The Population, Intervention, Comparator, Outcome, Study (PICOS) framework was used to develop the search strategy.

15.1 Search Strategy

The search strategy aimed to identify RCTs for biologic treatments for moderate-to-severe uncontrolled asthma (GINA 2019 step 4 and 5). The 2019 guidelines were used because the 2022 update was not available at the time of the design of the SLR (October 2020; updated in January 2022), and the earlier version of GINA would be more applicable to studies that have been completed and published as of this review. The SLR included a comprehensive database search and a targeted grey literature search. Results from grey literature sources were used to cross-reference the included studies identified through the database search.

15.2 Database Search

The Ovid® platform was used to search the following databases: MEDLINE®; MEDLINE® In-Process, and Other Non-Indexed Citations; Embase; and the Cochrane Central Register of Controlled Trials. Vocabulary and syntax were modified for each database searched. Search strategies used a combination of controlled vocabulary and keywords, such as “uncontrolled” and “asthma”. Filters pertaining to RCTs or SLRs and meta-analyses (MAs) were also applied. The database search was not restricted by outcomes, language, or publication date at the search stage. When possible, animal-only and opinion pieces were removed from the results. The database search was conducted in October 2020 and updated in January 2022. For an overview see Table 1 below.

In the database search update conducted in January 2022, 884 records were identified; an additional 947 were identified through grey literature searches and other sources (626 conference abstracts; 109 ClinicalTrials.gov records; 10 documents from HTA websites; and 202 records from the bibliography search). After removing duplicates, there were 1,618 additional records that were screened at the title and abstract stage and of these, 1,437 were excluded. Full texts of the remaining 181 records were obtained and assessed for eligibility. Of these, 120 records were excluded, with the most common reasons being a subgroup analysis not of interest, study design, and population. Details are shown in the PRISMA flow diagram for the updated search (Figure 15). In total, 61 records reporting results for 14 unique RCTs and three unique extension studies met the inclusion criteria. Four of these trials were newly identified in the updated search, as well as a new publication for BORA (the extension study of SIROCCO, CALIMA, and ZONDA). (4-8)

Table 77 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Ovid	1974 to January 19 2022	First conducted in October 2020, updated search conducted in January 2022
Medline®	Ovid	1946 to January 19 2022	First conducted in October 2020, updated search conducted in January 2022
MEDLINE® In-Process, and Other Non-Indexed Citations	Ovid	1946 to January 19 2022	First conducted in October 2020, updated search conducted in January 2022
Cochrane Central Register of Controlled Trials	Ovid	December 2021	First conducted in October 2020, updated search conducted in January 2022

15.3 Grey Literature and Hand-Searching

Additional grey literature searches were performed to supplement the database searches. Key clinical conferences that were not indexed in Embase were searched in January 2021 and updated in February 2022 (Table 2); these searches were conducted to identify relevant abstracts submitted to the last two cycles of these conferences (i.e., latest two congresses such as those held in last two years for annual congresses and last four years for biennial congresses). The following clinical conferences were searched: American Academy of Allergy, Asthma, and Immunology (AAAAI), European Academy of Allergy and Clinical Immunology (EAACI), and European Respiratory Society (ERS). As part of the February 2022 update, the 2022 session of ERS was searched; other conferences had not yet taken place at the time of the update search.

Table 78 Summary of key conferences and their index status in Embase

Year	AAAAI	EAACI	ERS	ATS
2020	Not indexed	Not indexed	Not indexed	Indexed
2019	Not indexed	Indexed	Indexed	Indexed
2021	Indexed	Indexed	Not Indexed	Indexed

Abbreviations: AAAAI = American Academy of Allergy, Asthma, and Immunology; ATS = American Thoracic Society; EAACI = European Academy of Allergy and Clinical Immunology; ERS = European Respiratory Society.

A targeted grey literature search of the US National Institutes of Health (NIH) ClinicalTrials.gov and searches of health technology assessment (HTA) websites (Canadian Agency for Drugs and Technologies in Health [CADTH] and National Institute for Health and Care Excellence [NICE]) were also completed to identify additional studies of interest. Hand-searches of the bibliographies of relevant SLRs, MAs, and network meta-analyses (NMAs; published within the last three years) identified from the database search were performed to identify additional relevant studies).

15.4 Eligibility Criteria

The pre-specified PICOS criteria described in table 3 were used to identify relevant studies for inclusion in this review. The scope of the SLR focused on RCTs of key biologic treatments for adult patients with moderate-to-severe uncontrolled asthma, which was defined as remaining uncontrolled despite adherence to maximally optimized GINA 2019 Step 4 or 5 treatment (i.e., either at least medium dose ICS plus LABA or another controller medication, or high dose ICS alone).(9) Besides tezepelumab, key treatments, at the approved dosages (based on prescribing information from the FDA(10-14), EMA(15-19), and Japan), included: omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab. In addition, key subgroup analyses of relevant trials were included. Subgroup analyses that were deemed not of interest were excluded. Pooled analyses of relevant trials were also excluded in a separate category, with the potential to be revisited if additional data are required for future analyses. Records that did not provide enough information for inclusion based on the PICOS criteria (i.e., dosing) were excluded based on insufficient information. Although the search was not restricted by language, non-English articles were excluded at the full-text screening phase. Study selection was not limited by outcomes or publication date.

Based on the results of initial screening, the PICOS criterion related to use of GINA 2019 Step 4/5 therapies was relaxed to permit inclusion of studies that reported LABA use (in combination with at least medium dose ICS) among at least 75% of enrolled patients, even if LABA use or other controllers were not required as a part of the trial eligibility inclusion criteria. This was done to avoid exclusion of key comparator trials (i.e., reslizumab trials) and for consistency with past SLRs. (20-24)

Table 79. Summary of inclusion and exclusion criteria for the literature search

Criterion	Inclusion Criteria	Exclusion Criteria
Population	Patients at least 12 years of age who have asthma that remains uncontrolled despite adherence with maximal optimized GINA 2019 Step 4 or 5 treatment, including medium to high dose ICS and LABA[a]	Mild disease severity only Other respiratory disease without asthma included Non-human studies All patients under the age of 12
Intervention	Tezepelumab (210 mg every four weeks)	None
Comparators	**Approved dosages of the following based on prescribing information from FDA, EMA, and/or Japan[b]:** **Anti-IgE**	Other treatments not listed in inclusion criteria Treatments or doses not indicated/approved for the population of interest

Criterion	Inclusion Criteria	Exclusion Criteria
	• Omalizumab (75 to 375 mg [FDA and Japan] or 600 mg [EMA] every 2 or 4 weeks; dose and frequency determined by baseline IgE level and body weight [kg])(18); (11) Anti-IL-5 pathways • Mepolizumab (100 mg every 4 weeks)(17); (10) • Reslizumab (3 mg/kg once every 4 weeks)(19); (12) • Benralizumab (30 mg every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter)(15); (13) Anti-IL-4/IL-13 • Dupilumab (An initial dose of 400 mg [two 200 mg injections] followed by 200 mg given every other week or an initial dose of 600 mg [two 300 mg injections] followed by 300 mg given every other week)(16); (14)	Non-pharmacological interventions
Outcomes	Efficacy, safety, and patient-reported outcomes including (but not limited to): • Exacerbation rate reduction • Exacerbations leading to hospital/ER visits • Reduction in OCS use • Improvements in quality of life (e.g., generic measures such as EQ-5D and SF-36, and disease specific measures such as AQLQ, SGRQ, cough assessments, and impact specific PROs) • Response to treatment • Discontinuation of treatment • Reduction in biomarkers (e.g., blood eosinophils, IgE, FeNO)	None
Study Design	• RCTs reported in peer-reviewed publications, conference abstracts/posters, or grey literature • Systematic reviews, meta-analyses, and network meta-analyses[c]	Non-RCTs Single-arm studies Study protocols Opinion pieces, commentaries, letters, editorials, case reports Economic/cost-effectiveness evaluations Narrative reviews (i.e., non-systematic)
Location	• Global	None
Language	• English only[d]	Non-English
Publication date	• No restriction: From the inception of the databases to date of search; additionally, regular alerts will be established	None

[a] This criterion was relaxed after initial screening to permit inclusion of studies in which at least 75% of patients reported LABA use (plus at least medium dose ICS), despite not requiring use of LABA or other controllers as a part of their inclusion criteria.
[b] Latest version of Japan prescribing information (as for March 2020)
[c] Systematic reviews, meta-analyses, network meta-analyses, and the bibliographies of these records were reviewed and cross-referenced with the included study lists to ensure that no primary studies were missed.
[d] Search captured all languages, but non-English citations were excluded during full-text screening.

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; EMA = European Medicines Agency; ER = emergency room; EQ-5D = EuroQol-5 Dimensions; FDA = Food and Drug Administration; FeNO = fractional exhaled nitric oxide; ICS = inhaled corticosteroid; IgE = immunoglobulin E; IL = interleukin; kg = kilogram; LABA = Long-Acting β-Agonist; mg = milligram; PRO = patient reported outcome; RCT = randomized controlled trial; SF-36 = 36-Item Short Form Health Survey; SGRQ = St. George's Respiratory Questionnaire.

Table 80: Key subgroups of interest

Subgroups of Interest
Patients with ≥3 exacerbations in the past year[a]
High EOS counts (eligible for IL-5 or IL-4 therapies) • ≥150 cells/µL • ≥300 cells/µL
Low EOS counts EOS ≤150 cells/µL EOS ≤300 cells/µL
High FeNO counts (eligible for IL-4 therapy) • ≥25 ppb • ≥50 ppb
Patients with OCS-dependent asthma and EOS count more than 150 cells/ µL Patients with OCS-dependent asthma and EOS count less than 300 cells/ µL Patients with OCS-dependent asthma and EOS count more than 300 cells/ µL
High EOS and FeNO counts (eligible for IL-4 therapy) ≥150 cells/µL and FeNO ≥25 ppb ≥150 cells/µL and FeNO ≥50 ppb ≥300 cells/µL and FeNO ≥25 ppb ≥300 cells/µL and FeNO ≥50 ppb
Allergic asthma (i.e., high IgE) – eligible for anti-IgE therapy
Triple-positive patients (high EOS, high FeNO, and high IgE counts) • EOS ≥150 cells/µL and FeNO ≥25 ppb with allergic asthma • EOS ≥300 cells/µL and FeNO ≥25 ppb with allergic asthma • EOS ≥150 cells/µL and FeNO ≥50 ppb with allergic asthma • EOS ≥300 cells/µL and FeNO ≥50 ppb with allergic asthma
Patients not eligible for any current biologic treatment Low EOS (<150 cells/µL) and FeNO (<25 ppb) counts
Patients that switched from other biologic treatments

[a] Definition of severe asthma within the UK
Abbreviations: EOS = eosinophils; FeNO = fractional exhaled nitric oxide; ICS = inhaled corticosteroid; IgE = immunoglobulin E; IL = interleukin; ppb = parts per billion; OCS = oral corticosteroid; UK = United Kingdom; µL = microliter.

Table 81 EBM Reviews - Cochrane Central Register of Controlled Trials December 2021, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to January 12, 2022, Embase 1974 to 2022 January 19, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to January 19, 2022

No.	Query	Results
#1	asthma/ or (asthma$ adj3 (sever$ or persisten$ or uncontrol$ or "not control$" or "no control$" or (lack$ adj2 control$) or "GINA step 4" or "GINA step 5" or "GINA 4" or "GINA 5" or ("Global Initiative for Asthma" adj2 ("step 4" or "step 5")))).ti,ab,kw,kf.	407489

No.	Query	Results
#2	(asthma/ and recurrence/) or (asthma$ adj3 (recurren$ or refract$ or recrudescen$ or ((fail$ or lack$) adj2 respon$) or nonrespon$ or non-respon$ or unrespon$ or un-respon$ or "no respon$" or "not respon$" or reappear$ or re-appear$ or reoccur$ or re-occur$)).ti,ab,kw,kf.	9619
#3	1 or 2	409003
#4	(tezepelumab or "amg 157" or amg157 or medi9929 or "medi 9929" or "1572943 04 4" or "DB15090" or "RJ1IW3B4QX").ti,ab,kw,kf,rn.	500
#5	omalizumab/ or (omalizumab or olizumab$2 or "242138 07 4" or "fb 317" or fb317 or "gbr 310" or gbr310 or "hu 901" or hu901 or "rg 3648" or rg3648 or "rhumab 25" or "rhumab e25" or "sti 004" or sti004 or "syn 008" or syn008 or Xolair$2).ti,ab,kw,kf,rn.	14111
#6	(mepolizumab or bosatria$2 or nucala$2 or "sb 240563" or sb240563 or "196078 29 2").ti,ab,kw,kf,rn.	5003
#7	(reslizumab or cinqaero$2 or cinqair$2 or "sch 55700" or sch55700 or "cep 38072" or cep38072 or dcp835 or "dcp 835" or "241473 69 8").ti,ab,kw,kf,rn.	1790
#8	(benralizumab or fasenra$2 or "medi 563" or medi563 or "BIW 8405" or "1044511 01 4").ti,ab,kw,kf,rn.	2350
#9	(dupilumab or dupixent$2 or "regn 668" or regn668 or "sar 231893" or sar231893 or "1190264 60 8").ti,ab,kw,kf,rn.	5557
#10	4 or 5 or 6 or 7 or 8 or 9	23056
#11	randomized controlled trial/ or controlled clinical trial/ or (randomized or placebo or randomly or trial or groups).ab. or drug therapy.fs. [RANDOMIZED STUDIES – MEDLINE sensitive Filter – Cochrane Handbook, 2019]	14302197
#12	3 and 10 and 11	8441
#13	12 use ppez	1710
#14	asthma/ or severe persistent asthma/ or (asthma$ adj3 (sever$ or persisten$ or uncontrol$ or "not control$" or "no control$" or (lack$ adj2 control$) or "GINA step 4" or "GINA step 5" or "GINA 4" or "GINA 5" or ("Global Initiative for Asthma" adj2 ("step 4" or "step 5")))).ti,ab,kw.	407503
#15	(asthma/ and relapse/) or (asthma$ adj3 (recurren$ or refract$ or recrudescen$ or ((fail$ or lack$) adj2 respon$) or nonrespon$ or non-respon$ or unrespon$ or un-respon$ or "no respon$" or "not respon$" or reappear$ or re-appear$ or reoccur$ or re-occur$)).ti,ab,kw.	9183
#16	14 or 15	409014
#17	tezepelumab/ or (tezepelumab$2 or "amg 157" or amg157 or medi9929 or "medi 9929" or "1572943 04 4" or "DB15090" or "RJ1IW3B4QX").ti,ab,kw,du,dy,tn,rn.	510

No.	Query	Results
#18	omalizumab/ or (omalizumab or olizumab$2 or "242138 07 4" or "fb 317" or fb317 or "gbr 310" or gbr310 or "hu 901" or hu901 or "rg 3648" or rg3648 or "rhumab 25" or "rhumab e25" or "sti 004" or sti004 or "syn 008" or syn008 or Xolair$2).ti,ab,kw,du,dy,tn,rn.	14112
#19	mepolizumab/ or (mepolizumab or bosatria$2 or nucala$2 or "sb 240563" or sb240563 or "196078 29 2").ti,ab,kw,du,dy,tn,rn.	4996
#20	reslizumab/ or (reslizumab or cinqaero$2 or cinqair$2 or "sch 55700" or sch55700 or "cep 38072" or cep38072 or dcp835 or "dcp 835" or "241473 69 8").ti,ab,kw,du,dy,tn,rn.	1844
#21	benralizumab/ or (benralizumab or fasenra$2 or "medi 563" or medi563 or "BIW 8405" or "1044511 01 4").ti,ab,kw,du,dy,tn,rn.	2367
#22	dupilumab/ or (dupilumab or dupixent$2 or "regn 668" or regn668 or "sar 231893" or sar231893 or "1190264 60 8").ti,ab,kw,du,dy,tn,rn.	5555
#23	17 or 18 or 19 or 20 or 21 or 22	23063
#24	Randomized controlled trial/ or Controlled clinical study/ or randomization/ or intermethod comparison/ or double blind procedure/ or human experiment/ or (compare or compared or comparison or trial).ti. or ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. or (random$ or placebo or (open adj label) or ((double or single or doubly or singly) adj (blind or blinded or blindly)) or parallel group$1 or (crossover or cross over) or ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)) or (assigned or allocated) or (controlled adj7 (study or design or trial)) or (volunteer or volunteers)).ti,ab.	10648938
#25	(Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)) or ((((case adj control$) and random$) not randomi?ed controlled) or (nonrandom$ not random$) or "Random field$" or (random cluster adj3 sampl$)).ti,ab. or (Systematic review not (trial or study)).ti. or ((review.ab. and review.pt.) not trial.ti.) or ("we searched".ab. and (review.ti. or review.pt.)) or ("update review" or (databases adj4 searched)).ab. or ((rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/) or (Animal experiment/ not (human experiment/ or human/))	5433779
#26	24 not 25 [RANDOMIZED STUDIES – Embase sensitive Filter – Cochrane Handbook, 2019]	9730676
#27	16 and 23 and 26	3454
#28	27 use oemezd	1932
#29	asthma/ or (asthma$ adj3 (sever$ or persisten$ or uncontrol$ or "not control$" or "no control$" or (lack$ adj2 control$) or "GINA step 4" or "GINA step 5" or "GINA 4" or "GINA 5" or ("Global Initiative for Asthma" adj2 ("step 4" or "step 5")))).ti,ab,kw.	407441

No.	Query	Results
#30	(asthma/ and recurrence/) or (asthma$ adj3 (recurren$ or refract$ or recrudescen$ or ((fail$ or lack$) adj2 respon$) or nonrespon$ or non-respon$ or unrespon$ or un-respon$ or "no respon$" or "not respon$" or reappear$ or re-appear$ or reoccur$ or re-occur$)).ti,ab,kw.	9589
#31	29 or 30	408954
#32	(tezepelumab$2 or "amg 157" or amg157 or medi9929 or "medi 9929" or "1572943 04 4" or "DB15090" or "RJ1IW3B4QX").ti,ab,kw.	285
#33	omalizumab/ or (omalizumab or olizumab$2 or "242138 07 4" or "fb 317" or fb317 or "gbr 310" or gbr310 or "hu 901" or hu901 or "rg 3648" or rg3648 or "rhumab 25" or "rhumab e25" or "sti 004" or sti004 or "syn 008" or syn008 or Xolair$2).ti,ab,kw.	14097
#34	(mepolizumab or bosatria$2 or nucala$2 or "sb 240563" or sb240563 or "196078 29 2").ti,ab,kw.	3061
#35	(reslizumab or cinqaero$2 or cinqair$2 or "sch 55700" or sch55700 or "cep 38072" or cep38072 or dcp835 or "dcp 835" or "241473 69 8").ti,ab,kw.	955
#36	(benralizumab or fasenra$2 or "medi 563" or medi563 or "BIW 8405" or "1044511 01 4").ti,ab,kw.	1571
#37	(dupilumab or dupixent$2 or "regn 668" or regn668 or "sar 231893" or sar231893 or "1190264 60 8").ti,ab,kw.	4361
#38	32 or 33 or 34 or 35 or 36 or 37	21452
#39	31 and 38	10724
#40	39 use cctr	1140
#41	exp Animals/ not (exp Animals/ and Humans/)	17082325
#42	(editorial or letter).pt. not (letter.pt. and randomized controlled trial/)	3674909
#43	13 not (41 or 42) [Animal studies & Opinion publications removed - Medline records]	1501
#44	exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/	54512218
#45	exp human/ or exp human experimentation/ or exp human experiment/	43870126
#46	(editorial or note or short survey).pt.	2549164
#47	28 not ((44 not 45) or 46) [Animal studies & Opinion publications removed - Embase records]	1889
#48	40 or 43 or 47	4530
#49	limit 48 to dt="20201001-20221231" [Update for 01 Oct 2020 - Current]	3228
#50	49 use ppez	199

No.	Query	Results
#51	limit 48 to dc="20201001-20221231" [Update for 01 Oct 2020 - Current]	1551
#52	51 use oemezd	411
#53	48 and (202008* or 202009* or 202010* or 202011* or 202012* or 2021* or 2022*).up. [Update for 01 Aug 2020 - Current]	2391
#54	53 use cctr	534
#55	50 or 52 or 54	1144
#56	limit 55 to yr="2020 -Current" [All databases - RCTs]	821
#57	**remove duplicates from 56 [All databases -deduplicated- RCTs]**	**652**
#58	asthma/ or (asthma$ adj3 (sever$ or persisten$ or uncontrol$ or "not control$" or "no control$" or (lack$ adj2 control$) or "GINA step 4" or "GINA step 5" or "GINA 4" or "GINA 5" or ("Global Initiative for Asthma" adj2 ("step 4" or "step 5")))).ti,ab,kw,kf.	407489
#59	(asthma/ and recurrence/) or (asthma$ adj3 (recurren$ or refract$ or recrudescen$ or ((fail$ or lack$) adj2 respon$) or nonrespon$ or non-respon$ or unrespon$ or un-respon$ or "no respon$" or "not respon$" or reappear$ or re-appear$ or reoccur$ or re-occur$)).ti,ab,kw,kf.	9619
#60	58 or 59	409003
#61	(tezepelumab$2 or "amg 157" or amg157 or medi9929 or "medi 9929" or "1572943 04 4" or "DB15090" or "RJ1IW3B4QX").ti,ab,kw,kf,rn.	500
#62	omalizumab/ or (omalizumab or olizumab$2 or "242138 07 4" or "fb 317" or fb317 or "gbr 310" or gbr310 or "hu 901" or hu901 or "rg 3648" or rg3648 or "rhumab 25" or "rhumab e25" or "sti 004" or sti004 or "syn 008" or syn008 or Xolair$2).ti,ab,kw,kf,rn.	14111
#63	(mepolizumab or bosatria$2 or nucala$2 or "sb 240563" or sb240563 or "196078 29 2").ti,ab,kw,kf,rn.	5003
#64	(reslizumab or cinqaero$2 or cinqair$2 or "sch 55700" or sch55700 or "cep 38072" or cep38072 or dcp835 or "dcp 835" or "241473 69 8").ti,ab,kw,kf,rn.	1790
#65	(benralizumab or fasenra$2 or "medi 563" or medi563 or "BIW 8405" or "1044511 01 4").ti,ab,kw,kf,rn.	2350
#66	(dupilumab or dupixent$2 or "regn 668" or regn668 or "sar 231893" or sar231893 or "1190264 60 8").ti,ab,kw,kf,rn.	5557
#67	61 or 62 or 63 or 64 or 65 or 66	23056
#68	(systematic review or systematic literature review or systematic scoping review or systematic narrative review or systematic qualitative review or systematic evidence review or systematic quantitative review or "systematic meta-review" or systematic critical review or systematic mixed studies review or systematic mapping review or systematic cochrane review or "systematic search	240402

No.	Query	Results
	and review" or systematic integrative review).ti. not comment.pt. not (protocol or protocols).ti. not MEDLINE.st.	
#69	(1469-493X or 1361-6137).is. and review.pt.	31485
#70	systematic review.pt.	191250
#71	68 or 69 or 70	447317
#72	60 and 67 and 71	152
#73	72 use ppez	70
#74	asthma/ or severe persistent asthma/ or (asthma$ adj3 (sever$ or persisten$ or uncontrol$ or "not control$" or "no control$" or (lack$ adj2 control$) or "GINA step 4" or "GINA step 5" or "GINA 4" or "GINA 5" or ("Global Initiative for Asthma" adj2 ("step 4" or "step 5")))).ti,ab,kw.	407503
#75	(asthma/ and relapse/) or (asthma$ adj3 (recurren$ or refract$ or recrudescen$ or ((fail$ or lack$) adj2 respon$) or nonrespon$ or non-respon$ or unrespon$ or un-respon$ or "no respon$" or "not respon$" or reappear$ or re-appear$ or reoccur$ or re-occur$)).ti,ab,kw.	9183
#76	74 or 75	409014
#77	tezepelumab/ or (tezepelumab$2 or "amg 157" or amg157 or medi9929 or "medi 9929" or "1572943 04 4" or "DB15090" or "RJ1IW3B4QX").ti,ab,kw,du,dy,tn,rn.	510
#78	omalizumab/ or (omalizumab or olizumab$2 or "242138 07 4" or "fb 317" or fb317 or "gbr 310" or gbr310 or "hu 901" or hu901 or "rg 3648" or rg3648 or "rhumab 25" or "rhumab e25" or "sti 004" or sti004 or "syn 008" or syn008 or Xolair$2).ti,ab,kw,du,dy,tn,rn.	14112
#79	mepolizumab/ or (mepolizumab or bosatria$2 or nucala$2 or "sb 240563" or sb240563 or "196078 29 2").ti,ab,kw,du,dy,tn,rn.	4996
#80	reslizumab/ or (reslizumab or cinqaero$2 or cinqair$2 or "sch 55700" or sch55700 or "cep 38072" or cep38072 or dcp835 or "dcp 835" or "241473 69 8").ti,ab,kw,du,dy,tn,rn.	1844
#81	benralizumab/ or (benralizumab or fasenra$2 or "medi 563" or medi563 or "BIW 8405" or "1044511 01 4").ti,ab,kw,du,dy,tn,rn.	2367
#82	dupilumab/ or (dupilumab or dupixent$2 or "regn 668" or regn668 or "sar 231893" or sar231893 or "1190264 60 8").ti,ab,kw,du,dy,tn,rn.	5555
#83	77 or 78 or 79 or 80 or 81 or 82	23063
#84	((exp Meta Analysis/ or ((meta adj analy$) or metaanalys$ or (systematic adj (review$1 or overview$1))).tw. or (cancerlit or cochrane or embase or (psychlit or psyclit) or (psychinfo or psycinfo) or (cinahl or cinhal) or science citation index or bids).ab. or (reference lists or bibliograph$ or hand-search$ or manual search$ or relevant journals).ab. or ((data extraction or selection criteria).ab. and review.pt.)) not letter.pt.) or editorial.pt. or ((exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp	12925110

No.	Query	Results
	vertebrate/) not (exp human/ or exp human experimentation/ or exp human experiment/)) [Scottish Intercollegiate Guidelines Network (SIGN) SR and MA filter - specificity- Embase]	
#85	76 and 83 and 84	884
#86	85 use oemezd	675
#87	(asthma$ adj3 (sever$ or persisten$ or uncontrol$ or "not control$" or "no control$" or (lack$ adj2 control$) or "GINA step 4" or "GINA step 5" or "GINA 4" or "GINA 5" or ("Global Initiative for Asthma" adj2 ("step 4" or "step 5")))).ti,ab,kw.	69621
#88	(asthma$ adj3 (recurren$ or refract$ or recrudescen$ or ((fail$ or lack$) adj2 respon$) or nonrespon$ or non-respon$ or unrespon$ or un-respon$ or "no respon$" or "not respon$" or reappear$ or re-appear$ or reoccur$ or re-occur$)).ti,ab,kw.	7269
#89	87 or 88	74131
#90	(tezepelumab$2 or "amg 157" or amg157 or medi9929 or "medi 9929" or "1572943 04 4" or "DB15090" or "RJ1IW3B4QX").ti,ab,kw.	285
#91	(omalizumab or olizumab$2 or "242138 07 4" or "fb 317" or fb317 or "gbr 310" or gbr310 or "hu 901" or hu901 or "rg 3648" or rg3648 or "rhumab 25" or "rhumab e25" or "sti 004" or sti004 or "syn 008" or syn008 or Xolair$2).ti,ab,kw.	9753
#92	(mepolizumab or bosatria$2 or nucala$2 or "sb 240563" or sb240563 or "196078 29 2").ti,ab,kw.	3061
#93	(reslizumab or cinqaero$2 or cinqair$2 or "sch 55700" or sch55700 or "cep 38072" or cep38072 or dcp835 or "dcp 835" or "241473 69 8").ti,ab,kw.	955
#94	(benralizumab or fasenra$2 or "medi 563" or medi563 or "BIW 8405" or "1044511 01 4").ti,ab,kw.	1571
#95	(dupilumab or dupixent$2 or "regn 668" or regn668 or "sar 231893" or sar231893 or "1190264 60 8").ti,ab,kw.	4361
#96	90 or 91 or 92 or 93 or 94 or 95	17265
#97	89 and 96	6543
#98	97 use coch	6
#99	exp Animals/ not (exp Animals/ and Humans/)	17082325
#100	(editorial or letter).pt. not (letter.pt. and randomized controlled trial/)	3674909
#101	73 not (99 or 100) [Animal studies & Opinion publications removed - Medline records]	70
#102	exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/	54512218
#103	exp human/ or exp human experimentation/ or exp human experiment/	43870126

No.	Query	Results
#104	(editorial or note or short survey).pt.	2549164
#105	86 not ((102 not 103) or 104) [Animal studies & Opinion publications removed - Embase records]	326
#106	98 or 101 or 105	402
#107	limit 106 to dt="20201001-20221231" [Update for 01 Oct 2020 - Current]	343
#108	107 use ppez	11
#109	limit 106 to dc="20201001-20221231" [Update for 01 Oct 2020 - Current]	58
#110	109 use oemezd	52
#111	106 and (202010* or 202011* or 202012* or 2021* or 2022*).up. [Update for 01 Oct 2020 - Current]	125
#112	111 use coch	3
#113	108 or 110 or 112	66
#114	limit 113 to yr="2020 -Current"	63
#115	**remove duplicates from 114 [All databases - deduplicated - SLRs]**	**52**
#116	57 or 115	685
#117	**remove duplicates from 116 [All results - deduplicated]**	**674**

EndNote deduplication removed 3 additional duplicates for a total of **671** citations.

15.5 Study selection

Study selection was completed using the systematic review software DistillerSR (Evidence Partners, Ontario, Canada).(25) After the removal of duplicates, citations identified in the database search were screened by two independent reviewers who assessed titles and abstracts according to the pre-specified PICOS criteria and subgroups of interest. Studies deemed eligible based on the title/abstract were then reviewed by two independent reviewers in full text to determine formal inclusion in the final review. During the full-text review, reasons for exclusion were documented by each reviewer. Any discrepancies between the two reviewers were resolved by consensus or were referred to and resolved by a third independent reviewer not involved in the data collection process.

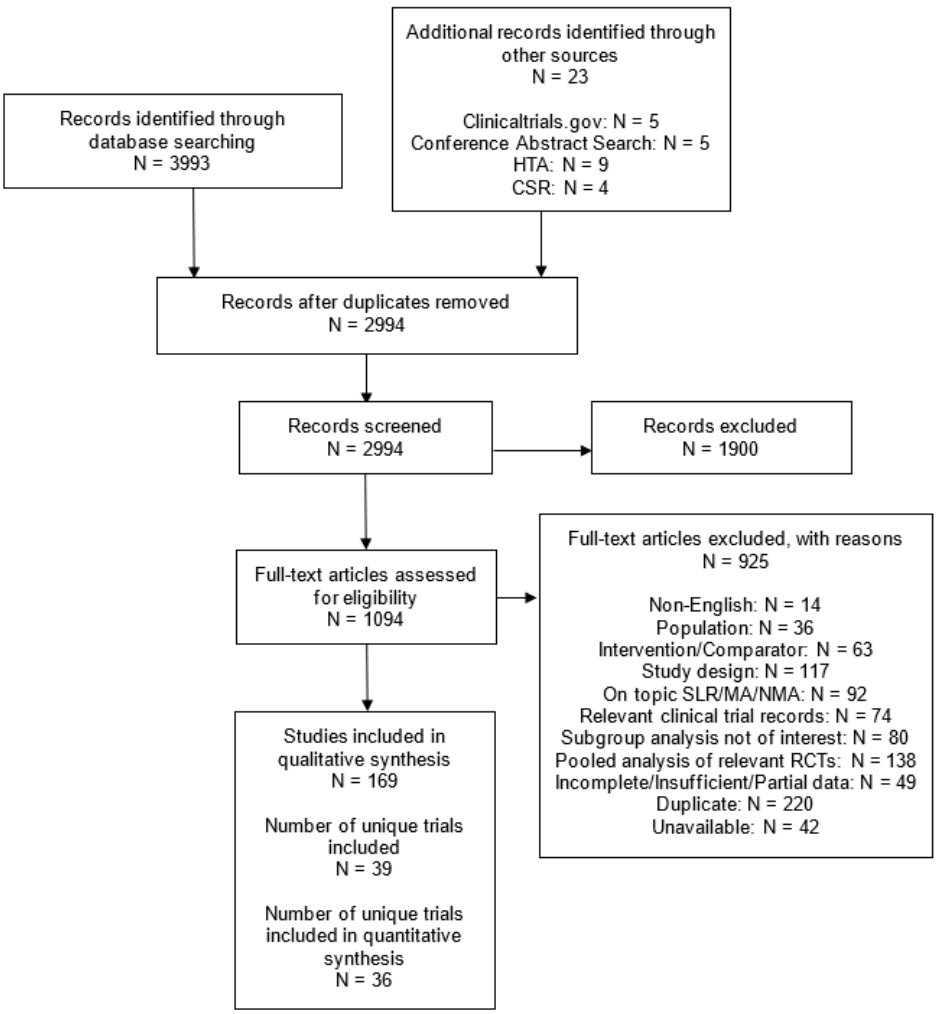
15.6 Clinical Evidence Search Results

The database search conducted in October 2020 identified 3,993 citations; an additional 23 records were identified through grey literature searches and other sources (five conference abstracts; five ClinicalTrials.gov records [four records were additional unique trials and one record was a full-text publication of a trial already captured in the database search]; nine documents from HTA websites; and four records pertaining to three clinical study reports (CSR) for NAVIGATOR, SOURCE, and PATHWAY provided by AstraZeneca.(26-29) After removing duplicates, the remaining 2,994 records were screened at the title and abstract stage and of these, 1,900 were excluded. Full texts of the remaining

1,094 records were obtained and assessed for eligibility. A total of 925 records were excluded for various reasons with the most common being duplicate studies, pooled analyses of relevant RCTs, and study design (i.e., not an RCT). Details are shown in the PRISMA flow diagram (Figure 15 and 16). In total, 169 records reporting results for 39 unique trials met the inclusion criteria.(20-22, 26, 27, 30-61) Of note, PATHWAY (a phase II trial evaluating tezepelumab) was among the unique trials captured in the database search.

In the database search update conducted in January 2022, 884 records were identified; an additional 947 were identified through grey literature searches and other sources (626 conference abstracts; 109 ClinicalTrials.gov records; 10 documents from HTA websites; and 202 records from the bibliography search). After removing duplicates, there were 1,618 additional records that were screened at the title and abstract stage and of these, 1,437 were excluded. Full texts of the remaining 181 records were obtained and assessed for eligibility. Of these, 120 records were excluded, with the most common reasons being a subgroup analysis not of interest, study design, and population. Details are shown in the PRISMA flow diagram for the updated search (Figure 16). In total, 61 records reporting results for 14 unique RCTs and three unique extension studies met the inclusion criteria. Four of these trials were newly identified in the updated search, as well as a new publication for BORA (the extension study of SIROCCO, CALIMA, and ZONDA). (4-8) A list of all citations excluded at the full-text stage (within the database search) with reasons for exclusion is provided in table 6.

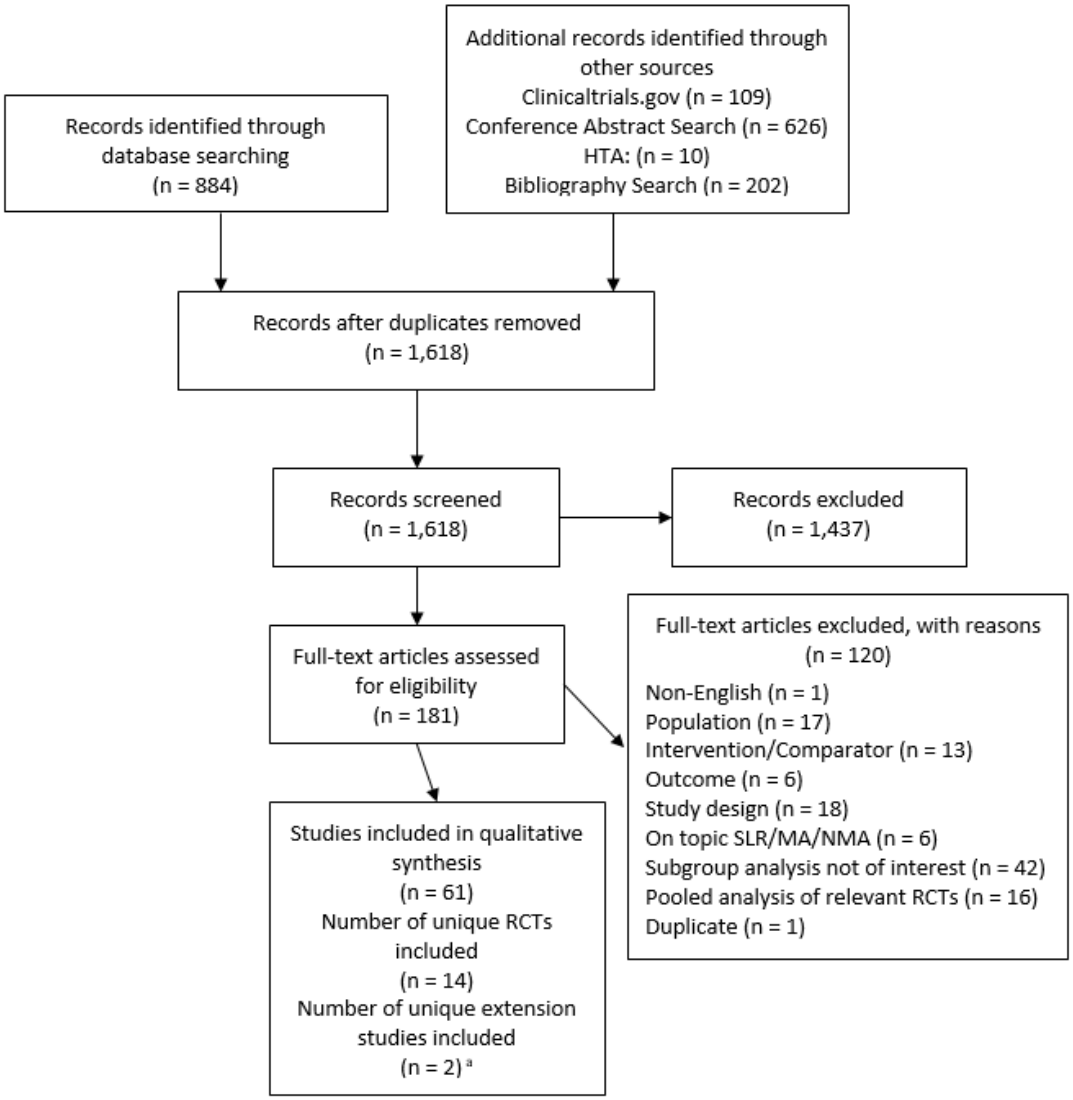
Figure 12 PRISMA flow diagram for clinical evidence for the original search (October 2020)



[a] Castro (2015) reports on two trials: trial NCT01287039 and trial NCT01285323(62)

Abbreviations: CSR = clinical study report; HTA = Health Technology Assessment; MA = meta-analysis; N = number; NMA = network meta-analysis; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = randomized controlled trial; SLR = systematic literature review.

Figure 13 PRISMA flow diagram for clinical evidence for the updated search (January 2022)



[a] A new publication for BORA (the extension study of SIROCCO, CALIMA, and ZONDA) was also identified, for a total of three unique extension studies between the original and update SLR.(8)

Abbreviations: HTA = Health Technology Assessment; MA = meta-analysis; n = number; NMA = network meta-analysis; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = randomized controlled trial; SLR = systematic literature review.

Table 82. A list of the excluded references/full text papers with a short reason

Study/Ref ID	Bibliography	Reason for exclusion
2	Pavord, Ian D, Bleecker, Eugene R, Buhl, Roland, Chanez, Pascal, Bel, Elisabeth H, Howarth, Peter, Bratton, Daniel J, Albers, Frank C, Yancey, Steven (2020//) Response to mepolizumab treatment is sustained across 4-weekly dosing periods.. ERJ open research 6 (3): #pages#. #notes#.	Intervention/Comparator
8	Virchow, J Christian, Hickey, Lisa, Du, Evelyn, Garin, Margaret (2020//) In patients with severe asthma with eosinophilia in reslizumab clinical trials, high peripheral blood eosinophil levels are associated with low FEV1 reversibility.. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology 16 (#issue#): 26. #notes#.	Duplicate
26	Tohda Y., Nakamura Y., Fujisawa T., Ebisawa M., Arima K., Miyata M., Takahashi Y., Rice M.S., Deniz Y., Rowe P., Patel N., Graham N.M.H., Teper A. (2020//) Dupilumab efficacy and safety in Japanese patients with uncontrolled, moderate-to-severe asthma in the phase 3 LIBERTY ASTHMA QUEST study. Allergology International 69 (4): 578. #notes#.	Subgroup analysis not of interest
29	Calzetta L., Ritondo B.L., Matera M.G., Facciolo F., Rogliani P. (2020//) Targeting IL-5 pathway against airway hyperresponsiveness: A comparison between benralizumab and mepolizumab. British Journal of Pharmacology 177 (20): 4750. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
37	Nelsen L.M., Cockle S.M., Gunsoy N.B., Jones P., Albers F.C., Bradford E.S., Mullerova H. (2020//) Impact of exacerbations on St George's Respiratory Questionnaire score in patients with severe asthma: post hoc analyses of two clinical trials and an observational study. Journal of Asthma 57 (9): 1006. #notes#.	Pooled analysis of relevant RCTs
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72	Emson C., Corren J., Saapa K., Hellqvist A., Parnes J.R., Colice G. (2020//) Effects of tezepelumab on asthma exacerbations and type 2 biomarkers in patients with severe, uncontrolled asthma with and without nasal polyps: Results from a post-hoc analysis of the phase 2b pathway study. American Journal of Respiratory and Critical Care Medicine 201 (1): #pages#. #notes#.	Subgroup analysis not of interest
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82	Busse W.W., Maspero J.F., Lu Y., Corren J., Hanania N.A., Chipps B.E., Katelaris C.H., FitzGerald J.M., Quirce S., Ford L.B., Rice M.S., Kamat S., Khan A.H.,	Subgroup analysis not of interest

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120	Bernstein J.A., Virchow J.C., Murphy K., Maspero J.F., Jacobs J., Adir Y., Humbert M., Castro M., Marsteller D.A., McElhattan J., Hickey L., Garin M., Vanlandingham R., Brusselle G. (2020//) Effect of fixed-dose subcutaneous reslizumab on asthma exacerbations in patients with severe uncontrolled asthma and corticosteroid sparing in patients with oral corticosteroid-dependent asthma: results from two phase 3, randomised, double-blind, placebo-controlled trials. The Lancet Respiratory Medicine 8 (5): 461. #notes#.	Intervention/Comparator
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154	Taille C., Israel E., Lee J., Gruber A., Smith S., Mallett S., Yancey S., Bradford E., Albers F., Liu M. (2020//) Seasonal efficacy of mepolizumab in patients with severe eosinophilic asthma - meta-analysis from two phase 3 trials. Journal of Allergy and Clinical Immunology 145 (2 Supplement): AB22. #notes#.	Pooled analysis of relevant RCTs
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164	Ambrose C., Colice G., Salapa K., Parnes J., Corren J. (2020//) Effect of Tezepelumab on Exacerbations in Patients with Severe, Uncontrolled Asthma, According to Baseline Body Mass Index: Results from the Phase 2b PATHWAY Study. Journal of Allergy and Clinical Immunology 145 (2 Supplement): AB25. #notes#.	Subgroup analysis not of interest
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166	Yancey S., Corren J., Price R., Castro M. (2020//) Exacerbation Reduction In Patients Based Upon Baseline Eosinophil Counts and FEV1 Reversibility. Journal of Allergy and Clinical Immunology 145 (2 Supplement): AB26. #notes#.	Intervention/Comparator
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173	Nair P., Bardin P., Humbert M., Murphy K.R., Hickey L., Garin M., Vanlandingham R., Chanez P. (2020//) Efficacy of Intravenous Reslizumab in Oral Corticosteroid-Dependent Asthma. Journal of Allergy and Clinical Immunology: In Practice 8 (2): 555. #notes#.	Pooled analysis of relevant RCTs
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186	(2020//) Exacerbation Reduction In Patients Based Upon Baseline Eosinophil Counts and FEV1 Reversibility. Exacerbation Reduction In Patients Based Upon Baseline Eosinophil Counts and FEV1 Reversibility 145 (2): AB26. #notes#.	Duplicate
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189	Corren J, Karpefors M, Hellqvist A, Parnes JR, Colice G (2020//) Seasonal variability of exacerbations in patients with severe, uncontrolled asthma and clinical benefits of tezepelumab: results from the pathway phase 2b study. #journal# 201 (1): #pages#. #notes#.	Subgroup analysis not of interest
190	Corren J, Ambrose C, Salapa K, Parnes JR, Pham T, Griffiths JM, Colice G (2020//) The effect of tezepelumab on exacerbations in patients with severe, uncontrolled asthma according to baseline serum IL-5 and IL-13 levels: results from the phase 2b pathway study. #journal# 201 (1): #pages#. #notes#.	Duplicate
191	Emson C, Corren J, Saapa K, Hellqvist A, Parnes JR, Colice G (2020//) Effects of tezepelumab on asthma exacerbations and type 2 biomarkers in patients with severe, uncontrolled asthma with and without nasal polyps: results from a post-hoc analysis of the phase 2b pathway study. #journal# 201 (1): #pages#. #notes#.	Duplicate

193	Moore WC, Kornmann O, Humbert M, Poirier C, Bel EH, Kaneko N, Smith SG, Martin N, Gilson MJ, Price RG, Bradford ES, Liu MC (2020//) Outcomes following continuation or stopping long-term mepolizumab treatment in patients with severe eosinophilic asthma: the randomized comet trial. #journal# 201 (1): #pages#. #notes#.	Duplicate
195	Pavord ID, Menzies Gow A, Bengtsson T, Peterson S, Fageras M, Garcia Gil E (2020//) Eosinophil counts and fractional exhaled nitric oxide levels after cessation of tezepelumab: results from the pathway phase 2b study. #journal# 201 (1): #pages#. #notes#.	Pooled analysis of relevant RCTs
196	Wechsler M, Ruddy MK, Pavord ID, Israel E, Rabe KF, Abdulai RM, Hu C, Martincova R, Nivens C, Amin N, Weinreich D, Yancopoulos G, Goulaouic H (2020//) Sar440340, an anti-il-33 monoclonal antibody, demonstrated a significant reduction of LOAC events and improved pre-BD FEV1 in patients with moderate to severe asthma: results from the phase 2 proof of concept study. #journal# 201 (1): #pages#. #notes#.	Intervention/Comparator
197	Wechsler ME, Hickey L, Garin M, Chauhan A (2020//) Efficacy of Reslizumab Treatment in Exacerbation-Prone Patients with Severe Eosinophilic Asthma. #journal# #volume# (#issue#): #pages#. #notes#.	Duplicate
198	NCT04502862 (2020//) Dupilumab Asthma Sleep Study. A Phase 4, Randomized, Double-blind, Placebo-controlled, Multicenter, Parallel-group Study of the Effect of Dupilumab on Sleep Disturbance in Patients With Uncontrolled Persistent Asthma #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
201	Kim M-K, Park H-S, Park C-S, Min S-J, Albers FC, Yancey SW, Mayer B, Kwon N (2020//) Efficacy and safety of mepolizumab in Korean patients with severe eosinophilic asthma from the DREAM and MENSA studies. #journal# #volume# (#issue#): #pages#. #notes#.	Duplicate
205	Lugogo NL, Kreindler JL, Martin UJ, Cook B, Hirsch I, Trudo FJ (2020//) Blood eosinophil count group shifts and kinetics in severe eosinophilic asthma. #journal# #volume# (#issue#): #pages#. #notes#.	Duplicate
206	Sheehan WJ, Krouse RZ, Calatroni A, Gergen PJ, Gern JE, Gill MA, Gruchalla RS, Khurana Hershey GK, Kattan M, Kercsmar CM, Lamm CI, Little FF, Makhija MM, Searing DA, Zoratti E, Busse WW, Teach SJ (2020//) Aeroallergen Sensitization, Serum IgE, and Eosinophilia as Predictors of Response to Omalizumab Therapy during the Fall Season among Children with Persistent Asthma. #journal# #volume# (#issue#): #pages#. #notes#.	Duplicate
207	Virchow JC, Hickey L, Du E, Garin M (2020//) In patients with severe asthma with eosinophilia in reslizumab clinical trials, high peripheral blood eosinophil levels are associated with low FEV1 reversibility. #journal# 16 (1): #pages#. #notes#.	Duplicate
208	Bernstein JA, Virchow JC, Murphy K, Maspero JF, Jacobs J, Adir Y, Humbert M, Castro M, Marsteller DA, McElhattan J, Hickey L, Garin M, Vanlandingham R, Brusselle G (2020//) Effect of fixed-dose subcutaneous reslizumab on asthma exacerbations in patients with severe uncontrolled asthma and corticosteroid sparing in patients with oral corticosteroid-dependent asthma: results from two phase 3, randomised, double-blind, placebo-controlled trials. #journal# #volume# (#issue#): #pages#. #notes#.	Duplicate
210	Li J, Yang J, Kong L, Huang Y, Chen P, Yan X, Liu X, Zho X, Liu J, Zhu X, Humphries M, Wang L, Pethe A, Wang X, Kottakis I, Fogel R, Zhong N (2020//) Efficacy and safety of omalizumab in patients with moderate-to-severe asthma: an analytic comparison of data from randomized controlled trials between Chinese and Caucasians. #journal# #volume# (#issue#): #pages#. #notes#.	Duplicate

212	Castro M, Rabe KF, Corren J, Pavord ID, Katelaris CH, Tohda Y, Zhang B, Rice MS, Maroni J, Rowe P, Pirozzi G, Amin N, Ruddy M, Akinlade B, Graham NMH, Teper A (2020//) Dupilumab improves lung function in patients with uncontrolled, moderate-to-severe asthma. #journal# 6 (1): #pages#. #notes#.	Duplicate
217	Carpagnano, Giovanna Elisiana, Sessa, Francesco, Scioscia, Giulia, Lacedonia, Donato, Foschino, Maria Pia, Venuti, Maria Pia, Triggiani, Antonio Ivano, Valenzano, Anna, Resta, Onofrio, Cibelli, Giuseppe, Messina, Giovanni (2019//) Physical Activity as a New Tool to Evaluate the Response to Omalizumab and Mepolizumab in Severe Asthmatic Patients: A Pilot Study.. Frontiers in pharmacology 10 (#issue#): 1630. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
251	Saglani, Sejal, Bush, Andrew, Carroll, Will, Cunningham, Steve, Fleming, Louise, Gaillard, Erol, Gupta, Atul, Murray, Clare, Nagakumar, Prasad, Paton, James, Roberts, Graham, Seddon, Paul, Sinha, Ian (2019//) Biologics for paediatric severe asthma: trick or TREAT?.. The Lancet. Respiratory medicine 7 (4): 294. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
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485	Passarell J., Jaworowicz D., Fiedler-Kelly J., Ludwig E., Marsteller D.A., Garin M., Rabinovich-Guilatt L. (2019//) Effect of reslizumab exposure on efficacy outcomes in a pharmacokinetic-pharmacodynamic (PK-PD) analysis of weight-based intravenous (IV) dosing. Allergy and Asthma Proceedings 40 (5): 359. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
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500	Kreindler J., Katial R., Barker P., Newbold P. (2019//) BENRALIZUMAB TREATMENT IS NOT ASSOCIATED WITH ORAL CORTICOSTEROID-LIKE INCREASES IN WEIGHT AND BLOOD PRESSURE. Annals of Allergy, Asthma and Immunology 123 (5 Supplement): S39. #notes#.	Pooled analysis of relevant RCTs
505	Silver J., Llanos J., Mayer B., Prazma C., Albers F. (2019//) GREATER EFFICACY OF MEPOLIZUMAB IN SEVERE EOSINOPHILIC ASTHMA WITH HIGH BASELINE BLOOD EOSINOPHIL COUNTS. Annals of Allergy, Asthma and Immunology 123 (5 Supplement): S37. #notes#.	Pooled analysis of relevant RCTs
509	Albers F., Howarth P., Bratton D., Yancey S., Bradford E., Kwon N. (2019//) Efficacy of mepolizumab in severe eosinophilic asthma by baseline eosinophil count and exacerbation history: Meta-analysis of two phase 3 trials. Allergy: European Journal of Allergy and Clinical Immunology 74 (Supplement 106): 455. #notes#.	On topic SLR/MA/NMA
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539	Hanania N., Castro M., Mirapeix C., BATEMAN E.R.I.C., Rice M., Djandji M., Ballard M., Rowe P., Deniz Y., Teper A. (2019//) DUPILUMAB REDUCES SEVERE EXACERBATIONS IN PATIENTS WITH ORAL CORTICOSTEROID-DEPENDENT SEVERE ASTHMA WITH AND WITHOUT EARLY IMPROVEMENTS IN LUNG FUNCTION. Chest 156 (4 Supplement): A929. #notes#.	Subgroup analysis not of interest
540	Carstens D., Liu M., Mitchell P., Smith S., Mallett S., Bradford E., Yancey S., Albers F. (2019//) EFFECT OF MEPOLIZUMAB ON EXACERBATIONS ACCORDING TO NUMBER AND TYPE OF BACKGROUND CONTROLLER THERAPIES: META-ANALYSIS FROM TWO PHASE 3 TRIALS. Chest 156 (4 Supplement): A1738. #notes#.	On topic SLR/MA/NMA
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550	Zangrilli J.G., Chipps B.E., Hirsch I., Trudo F., Alacqua M. (2019//) Demographics, Clinical Characteristics, and Response to benralizumab	Pooled analysis of relevant RCTs

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552	Zangrilli J.G., Wenzel S., Brusselle G., Hirsch I., Rastogi S. (2019//) Benralizumab Efficacy in patients with uncontrolled eosinophilic asthma by age at diagnosis. Pneumologie 73 (SUPPPL. 1): #pages#. #notes#.	Pooled analysis of relevant RCTs
553	Ortega H., Meyer E., Brusselle G., Asano K., Price R.G., Prazma C., Albers F., Yancey S., Gleich G. (2019//) Immunogenicity of Mepolizumab in Patients with Severe Eosinophilic Asthma: Experience from the clinical development program. Pneumologie 73 (SUPPPL. 1): #pages#. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
564	Katelaris C., Rabe K., Corren J., Langton D., Bardin P., Park H., Sher L., Zhang B., Amin N., Rodriguez A., Teper A. (2019//) Dupilumab improves asthma outcomes regardless of baseline lung function. Respirology 24 (Supplement 1): 110. #notes#.	Subgroup analysis not of interest
567	Maspero J.F., Corren J., Ford L.B., Sher L., Chipps B.E., Peters A.T., Rice M., Rowe P., Lu Y., Harel S., Staudinger H., Amin N., Ruddy M., Graham N.M.H., Teper A. (2019//) Dupilumab Suppresses Type 2 Biomarkers in Asthma Patients With and Without Comorbid Chronic Rhinosinusitis With or Without Nasal Polyposis (CRS/NP): Post Hoc Analysis of LIBERTY ASTHMA QUEST. Journal of Allergy and Clinical Immunology 143 (2 Supplement): AB98. #notes#.	Subgroup analysis not of interest
571	Busse W.W., Maspero J.F., Hanania N.A., FitzGerald J.M., Ford L.B., Rice M., Lu Y., Rowe P., Staudinger H., Amin N., Ruddy M., Graham N.M.H., Teper A. (2019//) Dupilumab Improves Lung Function and Reduces Severe Exacerbation Rate in Patients With Uncontrolled, Moderate-to-Severe Asthma With or Without Comorbid Allergic Rhinitis: Results From the Phase 3 LIBERTY ASTHMA QUEST Study. Journal of Allergy and Clinical Immunology 143 (2 Supplement): AB97. #notes#.	Subgroup analysis not of interest
572	Martinez S.O., Pedroza-Melendez A., Trejo-Uribe V., Bautista-Garcia S., Contreras-Verduzco A., Ramirez-Gonzalez E., Hernandez-Nieto L. (2019//) A Randomized, Open-label, Parallel-group Clinical Study to Evaluate the Efficacy and Safety of Omalizumab in the Treatment of Persistent Moderate and Severe Allergic Asthma and Persistent Allergic Rhinitis in Pediatric Patients 6 to 17 years of age. Journal of Allergy and Clinical Immunology 143 (2 Supplement): AB94. #notes#.	Incomplete/Insufficient/Partial data
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575	Hanania N.A., Corren J., Holweg C., Haselkorn T., Yang M., Lyon R.C., Iqbal A., Casale T.B. (2019//) Effects of Omalizumab on Blood Eosinophil Numbers in Patients with Allergic Asthma. Journal of Allergy and Clinical Immunology 143 (2 Supplement): AB95. #notes#.	Pooled analysis of relevant RCTs
578	Chanez P., Hickey L., Garin M., Castro M. (2019//) Evaluation of Eosinophilic Asthma Patients Without Blood Eosinophil (EOS) Response to Intravenous (IV) Reslizumab in a Post-Hoc Analysis of 52-Week Placebo-Controlled Phase 3 Studies. Journal of Allergy and Clinical Immunology 143 (2 Supplement): AB97. #notes#.	Pooled analysis of relevant RCTs

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582	Boguniewicz M., Thaci D., Lio P.A., Hultsch T., Rossi A.B., Eckert L., Gadkari A., Shumel B., Chen Q., Chen Z., Ardeleanu M. (2019//) Dupilumab Improves Outcomes of Concurrent Asthma and Chronic Sino-Nasal Conditions in Patients With Atopic Dermatitis-a Pooled Analysis of Four Phase 3 Studies (LIBERTY AD SOLO 1 & 2, CHRONOS, and CAFE). Journal of Allergy and Clinical Immunology 143 (2 Supplement): AB123. #notes#.	Pooled analysis of relevant RCTs
584	Ryan O., Bernstein D., Hirsch I., Kreindler J. (2019//) Pooled Baseline Characteristics of Women in Phase III Benralizumab Asthma Exacerbation Studies (SIROCCO and CALIMA). Journal of Allergy and Clinical Immunology 143 (2 Supplement): AB100. #notes#.	Pooled analysis of relevant RCTs
585	Vanlandingham R.G., Gubbi A., Corren J. (2019//) Variability In Absolute Blood Eosinophil (EOS) Counts Over 52 Weeks In Patients With Inadequately Controlled Eosinophilic Asthma Receiving Placebo In Two Duplicate Clinical Trials. Journal of Allergy and Clinical Immunology 143 (2 Supplement): AB98. #notes#.	Pooled analysis of relevant RCTs
586	Virchow J.C., Hickey L., Garin M. (2019//) High Peripheral Blood Eosinophil (EOS) Levels Are Associated With Low FEV1 Reversibility (REV) In Patients With Severe Eosinophilic Asthma. Journal of Allergy and Clinical Immunology 143 (2 Supplement): AB5. #notes#.	Pooled analysis of relevant RCTs
588	Bousquet J., Maspero J.F., Chipps B.E., Corren J., FitzGerald J.M., Chen Z., Lu Y., Rowe P., Staudinger H., Ruddy M., Graham N.M.H., Kamat S., Amin N., Teper A., Khan A. (2019//) Dupilumab Consistently Improves Rhinoconjunctivitis-Specific Health-Related Quality of Life in Patients With Uncontrolled, Moderate-to-Severe Asthma and Comorbid Allergic Rhinitis: Results from the Phase 3 LIBERTY ASTHMA QUEST Study. Journal of Allergy and Clinical Immunology 143 (2 Supplement): AB101. #notes#.	Subgroup analysis not of interest
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590	Bradford E.S., Taille C., Bratton D.J., Yancey S.W., Kwon N., Albers F., Papi A. (2019//) Efficacy Of 100 Mg SC Mepolizumab For Severe Eosinophilic Asthma (SEA) Across Body Weight: Meta-Analysis. Journal of Allergy and Clinical Immunology 143 (2 Supplement): AB102. #notes#.	On topic SLR/MA/NMA
591	Yancey S.W., Albers F., Bratton D.J., Bradford E.S., Kwon N., Chanez P., Licskai C., Quirce S. (2019//) Efficacy Of 100 Mg SC Mepolizumab For Severe Eosinophilic Asthma (SEA) Across Blood Eosinophil Counts: Meta-Analysis. Journal of Allergy and Clinical Immunology 143 (2 Supplement): AB101. #notes#.	On topic SLR/MA/NMA
594	(2019//) Dupilumab improved asthma control and health-related quality of life in patients with oral-corticosteroid-dependent severe asthma in the phase 3	Duplicate

	LIBERTY ASTHMA VENTURE study. Dupilumab improved asthma control and health-related quality of life in patients with oral-corticosteroid-dependent severe asthma in the phase 3 LIBERTY ASTHMA VENTURE study 199 (9): #pages#. #notes#.	
595	(2019//) Dupilumab reduces severe exacerbations and improves lung function regardless of baseline bronchodilator reversibility in patients with uncontrolled moderate-to-severe asthma enrolled in the LIBERTY ASTHMA QUEST study. Dupilumab reduces severe exacerbations and improves lung function regardless of baseline bronchodilator reversibility in patients with uncontrolled moderate-to-severe asthma enrolled in the LIBERTY ASTHMA QUEST study 199 (9): #pages#. #notes#.	Duplicate
600	(2019//) DUPILUMAB EFFICACY IN PATIENTS WITH UNCONTROLLED, MODERATE-TO-SEVERE ASTHMA AND SEROLOGIC EVIDENCE OF ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS. DUPILUMAB EFFICACY IN PATIENTS WITH UNCONTROLLED, MODERATE-TO-SEVERE ASTHMA AND SEROLOGIC EVIDENCE OF ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS 123 (5): S15. #notes#.	Duplicate
602	Sridhar S, Zhao W, Pham T-H, Kearley J, White WI, Wu Y, Parnes JR, Roskos LK, Griffiths JM (2019//) Tezepelumab decreases matrix remodelling and inflammatory pathways in patients with asthma. #journal# 54 (#issue#): #pages#. #notes#.	Duplicate
603	(2019//) Efficacy of omalizumab in reducing asthma exacerbation in asian patients: a pooled analysis of two randomized placebo-controlled studies. Efficacy of omalizumab in reducing asthma exacerbation in asian patients: a pooled analysis of two randomized placebo-controlled studies 199 (9): #pages#. #notes#.	Duplicate
604	(2019//) Dupilumab effect on lung function in patients with uncontrolled, moderate-to-severe asthma with an allergic phenotype. Dupilumab effect on lung function in patients with uncontrolled, moderate-to-severe asthma with an allergic phenotype 54 (#issue#): #pages#. #notes#.	Duplicate
605	(2019//) Clinical and histological impact of omalizumab in oral corticosteroid-dependent severe allergic asthma. Clinical and histological impact of omalizumab in oral corticosteroid-dependent severe allergic asthma 54 (#issue#): #pages#. #notes#.	Duplicate
606	Chanez P, McDonald M, Garin M, Murphy K (2019//) Early decreases in blood eosinophil levels with reslizumab. #journal# 143 (4): 1653. #notes#.	Pooled analysis of relevant RCTs
607	(2019//) Dupilumab Efficacy in Patients With Uncontrolled, Moderate-to-Severe Allergic Asthma. Dupilumab Efficacy in Patients With Uncontrolled, Moderate-to-Severe Allergic Asthma #volume# (#issue#): #pages#. #notes#.	Duplicate
609	(2019//) BENRALIZUMAB TREATMENT IS NOT ASSOCIATED WITH ORAL CORTICOSTEROIDa[Euro sign]"LIKE INCREASES IN WEIGHT AND BLOOD PRESSURE. BENRALIZUMAB TREATMENT IS NOT ASSOCIATED WITH ORAL CORTICOSTEROIDa[Euro sign]"LIKE INCREASES IN WEIGHT AND BLOOD PRESSURE 123 (5): S39. #notes#.	Duplicate
610	(2019//) Change in post-bronchodilator FEV 1 for patients with severe asthma with eosinophilic features following benralizumab therapy. Change in post-bronchodilator FEV 1 for patients with severe asthma with eosinophilic features following benralizumab therapy 74 (#issue#): 28. #notes#.	Duplicate
611	(2019//) Efficacy of omalizumab therapy in asthma patients with or without asthma-related and allergic comorbidities. Efficacy of omalizumab therapy in	Duplicate

	asthma patients with or without asthma-related and allergic comorbidities 74 (#issue#): 36. #notes#.	
612	(2019//) Dupilumab Efficacy in Patients with Uncontrolled, Moderate-to-Severe Allergic Asthma. Dupilumab Efficacy in Patients with Uncontrolled, Moderate-to-Severe Allergic Asthma #volume# (#issue#): #pages#. #notes#.	Duplicate
613	(2019//) Efficacy of Intravenous Reslizumab in Oral Corticosteroida[Euro sign]"Dependent Asthma. Efficacy of Intravenous Reslizumab in Oral Corticosteroida[Euro sign]"Dependent Asthma #volume# (#issue#): #pages#. #notes#.	Pooled analysis of relevant RCTs
614	(2019//) Dupilumab Suppresses Inflammatory Biomarkers in Asthma Patients With or Without Allergic Rhinitis: post Hoc Analysis of the LIBERTY ASTHMA QUEST Study. Dupilumab Suppresses Inflammatory Biomarkers in Asthma Patients With or Without Allergic Rhinitis: post Hoc Analysis of the LIBERTY ASTHMA QUEST Study 143 (2): AB97. #notes#.	Duplicate
615	(2019//) Dupilumab Improves Lung Function and Reduces Severe Exacerbation Rate in Patients With Uncontrolled, Moderate-to-Severe Asthma With or Without Comorbid Allergic Rhinitis: results From the Phase 3 LIBERTY ASTHMA QUEST Study. Dupilumab Improves Lung Function and Reduces Severe Exacerbation Rate in Patients With Uncontrolled, Moderate-to-Severe Asthma With or Without Comorbid Allergic Rhinitis: results From the Phase 3 LIBERTY ASTHMA QUEST Study 143 (2): AB97. #notes#.	Duplicate
616	(2019//) Dupilumab improved asthma control in patients with uncontrolled, moderate-to-severe asthma, regardless of exacerbations in the previous year. Dupilumab improved asthma control in patients with uncontrolled, moderate-to-severe asthma, regardless of exacerbations in the previous year 73 (SUPPPL. 1): #pages#. #notes#.	Duplicate
618	Mukherjee M, Kjarsgaard M, Radford K, Huang C, Leigh R, Dorscheid DR, Lemiere C, Boulet L-P, Waserman S, Martin J, Nair P (2019//) Omalizumab in patients with severe asthma and persistent sputum eosinophilia. #journal# 15 (1): #pages#. #notes#.	Duplicate
619	Park HS, Lee SH, Lee SY, Kim MK, Lee BJ, Werkstrom V, Barker P, Zangrilli JG (2019//) Efficacy and safety of benralizumab for Korean patients with severe, uncontrolled eosinophilic asthma. #journal# 11 (4): 508. #notes#.	Subgroup analysis not of interest
621	(2019//) Long-term Safety and Clinical Benefit of Mepolizumab in Patients With the Most Severe Eosinophilic Asthma: the COSMEX Study. Long-term Safety and Clinical Benefit of Mepolizumab in Patients With the Most Severe Eosinophilic Asthma: the COSMEX Study #volume# (#issue#): #pages#. #notes#.	Duplicate
622	(2019//) Safety of reslizumab in uncontrolled asthma with eosinophilia: a pooled analysis from six trials. Safety of reslizumab in uncontrolled asthma with eosinophilia: a pooled analysis from six trials #volume# (#issue#): #pages#. #notes#.	Duplicate
623	(2019//) Safety of Reslizumab in Uncontrolled Asthma with Eosinophilia: a Pooled Analysis from 6 Trials. Safety of Reslizumab in Uncontrolled Asthma with Eosinophilia: a Pooled Analysis from 6 Trials #volume# (#issue#): #pages#. #notes#.	Duplicate
624	Maspero JF, Rabe KF, Castro M, Rice MS, Rowe P, Deniz Y, Amin N, Kamat S, Teper A, Khan A (2019//) Dupilumab improves health-related quality of life in patients with oral corticosteroid dependent, severe asthma with comorbid chronic rhinosinusitis with and without nasal polyps. #journal# 74 (Suppl 106): 35. #notes#.	Duplicate

625	EUCTR2018-002501-53-PL (2019//) A Phase 3 extension study designed to evaluate the Safety and Tolerability of Tezepelumab in Adults and Adolescents with severe, uncontrolled asthma on Inhaled Corticosteroids and at least one additional asthma controller. A Multicentre, Double-blind, Randomized, Placebo Controlled, Parallel Group, Phase 3, Safety Extension Study to Evaluate the Safety and Tolerability of Tezepelumab in Adults and Adolescents with Severe Uncontrolled Asthma (DESTINATION) - DESTINATION #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
628	EUCTR2018-004588-30-PL (2019//) Tezepelumab Home Use Study. A Multicenter, Randomized, Open-label, Parallel group, Functionality, and Performance Study of an Accessorized Pre-filled Syringe and Autoinjector with Home-administered Subcutaneous Tezepelumab in Adolescent and Adult Subjects with Severe Asthma (PATH-HOME) - PATH-HOME #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
630	Castro M, Rabe KF, Kraft M, Corren J, Pavord ID, Katelaris C, Tohda Y, Rice MS, Lu Y, Rowe P, Staudinger HW, Amin N, Akinlade B, Graham NMH, Teper A (2019//) Dupilumab improved lung function in patients with uncontrolled, moderate-to-severe asthma. #journal# 199 (9): #pages#. #notes#.	Duplicate
631	Wechsler M, Hickey L, Garin MC, Chauhan A (2019//) Response rate improvement and systemic corticosteroid burden reduction with intravenous (IV) reslizumab in a subgroup of asthma patients with GINA 4/5 severity and >=2 clinical asthma exacerbations (CAEs) in the prior 12 months. #journal# 199 (9): #pages#. #notes#.	Duplicate
632	Corren J, Garcia Gil E, Parnes JR, Pham T, Griffiths JM (2019//) Tezepelumab treatment effect on annualized rate of exacerbations by baseline biomarkers in uncontrolled severe asthma patients: phase 2b PATHWAY study. #journal# 199 (9): #pages#. #notes#.	Duplicate
633	Corren J, Chen S, Callan L, Garcia Gil E (2019//) The impact of tezepelumab on hospitalization and emergency department visits in patients with severe uncontrolled asthma: results from the pathway phase 2b trial. #journal# 199 (9): #pages#. #notes#.	Duplicate
634	Pham T, Ren P, Parnes JR, Griffiths JM (2019//) Tezepelumab reduces multiple key inflammatory biomarkers in patients with severe, uncontrolled asthma in the phase 2b PATHWAY study. #journal# 199 (9): #pages#. #notes#.	Duplicate
637	Rabe KF, Castro M, Wenzel SE, Corren J, Pavord ID, Katelaris C, Tohda Y, Rice MS, Lu Y, Rowe P, Staudinger HW, Amin N, Akinlade B, Graham NMH, Teper A (2019//) Dupilumab improved lung function in patients with uncontrolled, moderate-to-severe asthma despite exacerbation events during the LIBERTY ASTHMA QUEST study. #journal# 199 (9): #pages#. #notes#.	Duplicate
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879	Perez De Llano L., Meizlik P., McDonald M., Mustafa S.S. (2018//) Reslizumab decreases nasal adverse events and upper respiratory-associated concomitant medication use in patients with eosinophilic asthma and nasal polyps. Allergy: European Journal of Allergy and Clinical Immunology 73 (Supplement 105): 91. #notes#.	Pooled analysis of relevant RCTs
886	Trudo F., Hirsch I., Gopalan G., Martin U. (2018//) Impact of body mass index on efficacy of benralizumab in patients with severe, uncontrolled eosinophilic asthma: Pooled analysis of the sirocco and calima trials. American Journal of Respiratory and Critical Care Medicine 197 (MeetingAbstracts): #pages#. #notes#.	Pooled analysis of relevant RCTs
887	Chipps B.E., Hirsch I., Trudo F., Alacqua M., Zangrilli J.G. (2018//) Demographics, clinical characteristics, and response to benralizumab treatment for patients with severe, eosinophilic asthma and fixed airflow obstruction. American Journal of Respiratory and Critical Care Medicine 197 (MeetingAbstracts): #pages#. #notes#.	Pooled analysis of relevant RCTs
891	Bleecker E.R., Wechsler M.E., Fitzgerald J.M., Menzies-Gow A., Wu Y., Hirsch I., Goldman M., Newbold P., Zangrilli J.G. (2018//) Influence of key clinical baseline factors on benralizumab efficacy for patients with severe, uncontrolled asthma. American Journal of Respiratory and Critical Care Medicine 197 (MeetingAbstracts): #pages#. #notes#.	Pooled analysis of relevant RCTs
895	Pahus L., Bourdin A., McDonald M., Meizlik P., Chanez P. (2018//) Up to four years of longitudinal follow-up for patients with severe eosinophilic asthma receiving reslizumab. American Journal of Respiratory and Critical Care Medicine 197 (MeetingAbstracts): #pages#. #notes#.	Subgroup analysis not of interest
896	Wechsler M., McDonald M., Garin M.C. (2018//) Reslizumab high-responder and super-responder asthma patients. American Journal of Respiratory and Critical Care Medicine 197 (MeetingAbstracts): #pages#. #notes#.	Pooled analysis of relevant RCTs
897	Albers F.C., Ortega H., Bradford E.S., Gilson M.J., Price R.G., Yancey S.W., Moore W.C. (2018//) Durability of clinical response following long-term treatment with mepolizumab in patients with severe eosinophilic asthma: The columba study. American Journal of Respiratory and Critical Care Medicine 197 (MeetingAbstracts): #pages#. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
899	Ortega H., Bradford E.S., Albers F.C., Gilson M.J., Price R.G., Yancey S.W., Leigh R., Khatri S. (2018//) Long-term safety of mepolizumab in patients with severe eosinophilic asthma: The columba study. American Journal of Respiratory and Critical Care Medicine 197 (MeetingAbstracts): #pages#. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
900	Bleecker E., McDonald M., Garin M.C. (2018//) Decreases in blood eosinophil levels correlate with lung function improvement with reslizumab treatment. American Journal of Respiratory and Critical Care Medicine 197 (MeetingAbstracts): #pages#. #notes#.	Pooled analysis of relevant RCTs
901	Maspero J.F., McDonald M., Garin M.C. (2018//) Higher baseline blood eosinophil levels are associated with greater improvement in quality of life with reslizumab treatment. American Journal of Respiratory and Critical Care Medicine 197 (MeetingAbstracts): #pages#. #notes#.	Pooled analysis of relevant RCTs
903	Murphy K.R., McDonald M., Garin M.C. (2018//) Improvements in exacerbation rate and lung function with weight-based intravenous reslizumab dosing in patients with baseline high body weight. American Journal of Respiratory and Critical Care Medicine 197 (MeetingAbstracts): #pages#. #notes#.	Duplicate

908	Liu M.C., Humbert M., Bratton D.J., Yancey S.W., Bradford E.S., Hozawa S., Albers F.C. (2018//) Effect of Mepolizumab (100 mg Subcutaneous) on Exacerbation Rate in Patients with Severe Eosinophilic Asthma by Omalizumab Eligibility (US Criteria), and Immunoglobulin E and Eosinophilic Subgroups. American Journal of Respiratory and Critical Care Medicine 197 (MeetingAbstracts): #pages#. #notes#.	On topic SLR/MA/NMA
909	Prazma C., Katial R., Howarth P.H., Bradford E., Ortega H., Yancey S. (2018//) Pharmacodynamic and clinical efficacy data from patient sputum subgroups in DREAM Treated with Mepolizumab Across a 10-Fold Dose Range. American Journal of Respiratory and Critical Care Medicine 197 (MeetingAbstracts): #pages#. #notes#.	Intervention/Comparator
911	Sadatsafavi M., Fitzgerald J., Safari A. (2018//) Heterogeneity in the rate and severity of exacerbations in severe eosinophilic asthma: Insight from a pooled analysis of two large clinical trials. American Journal of Respiratory and Critical Care Medicine 197 (MeetingAbstracts): #pages#. #notes#.	Pooled analysis of relevant RCTs
914	Shrimanker R., Pavord I.D., Price R., Bradford E.S., Keene O.N., Yancey S. (2018//) Fractional exhaled nitric oxide and the peripheral blood eosinophil count as biomarkers of the response to mepolizumab in patients with severe eosinophilic asthma. American Journal of Respiratory and Critical Care Medicine 197 (MeetingAbstracts): #pages#. #notes#.	Intervention/Comparator
915	Corren J., Parnes J.R., Wang L., Mo M., Roseti S.L., Griffiths J.M., O'Quinn S., Van Der Merwe R. (2018//) Improvements in asthma-related quality of life observed within 4 weeks of treatment with tezepelumab. American Journal of Respiratory and Critical Care Medicine 197 (MeetingAbstracts): #pages#. #notes#.	Duplicate
925	O'Quinn S., Xu X., Hirsch I., Gopalan G. (2018//) Patient-reported activity impairment, stress, and tiredness improvement in patients with severe, uncontrolled asthma with eosinophilic inflammation: Pooled results from two phase III trials of benralizumab. Pneumologie 72 (Supplement 1): #pages#. #notes#.	Pooled analysis of relevant RCTs
927	Ortega H., Albers F., Llanos J.P., Bardford E., Price G., Pouliquen I., Castro M. (2018//) Impact of weight on the efficacy of mepolizumab in patients with severe eosinophilic asthma. Pneumologie 72 (Supplement 1): #pages#. #notes#.	Pooled analysis of relevant RCTs
928	Roskos L., Wang B., Chia Y.L., Yu B., Barker P., Goldman M. (2018//) Relationship between benralizumab exposure and asthma exacerbation rate for patients with severe asthma. Pneumologie 72 (Supplement 1): #pages#. #notes#.	Duplicate
929	Roskos L., Wang B., Yan L., Yu B., Barker P., Goldman M. (2018//) Longitudinal modeling of prebronchodilator FEV1 response to benralizumab for patients with severe asthma. Pneumologie 72 (Supplement 1): #pages#. #notes#.	Pooled analysis of relevant RCTs
930	Chipps B.E., Newbold P., Hirsch I., Trudo F., Goldman M. (2018//) Efficacy of benralizumab for patients with severe, uncontrolled atopic asthma by serum immunoglobulin e concentrations. Pneumologie 72 (Supplement 1): #pages#. #notes#.	Pooled analysis of relevant RCTs
931	Newbold P., Hirsch I., Trudo F., Goldman M. (2018//) Effects of immunoglobin e concentration, eosinophil concentration, and atopy status on benralizumab efficacy in asthma. Pneumologie 72 (Supplement 1): #pages#. #notes#.	Pooled analysis of relevant RCTs
933	Weinstein S., Staudinger H., Guillonneau S., Taniou C., Eckert L., Maroni J., Rowe P., Amin N., Pirozzi G., Graham N., Teper A. (2018//) Dupilumab improves FEV1 and exacerbations in asthma with allergic rhinitis. Respirology 23 (Supplement 1): 154. #notes#.	Subgroup analysis not of interest

936	Akhbari M., Kneale D., Harris K.M., Pike K.C. (2018//) Interventions for autumn exacerbations of asthma in children: A systematic review. Archives of Disease in Childhood 103 (Supplement 1): A188. #notes#.	Incomplete/Insufficient/Partial data
937	Fahrenholz J.M., McDonald M., Garin M. (2018//) Association between asthma exacerbations and lung function with reslizumab treatment in patients with uncontrolled eosinophilic asthma: Pooled analysis of two phase 3 trials. Journal of Allergy and Clinical Immunology 141 (2 Supplement 1): AB17. #notes#.	Pooled analysis of relevant RCTs
938	Ortega H., Menzies-Gow A., Llanos-Ackert J.-P., Forshag M.S., Albers F.C., Gunsoy N., Bradford E., Yancey S.W., Kraft M. (2018//) Improvement of lung function measured by AM PEF in patients with severe eosinophilic asthma treated with mepolizumab: A combined analysis of the MENSA and MUSCA studies. Journal of Allergy and Clinical Immunology 141 (2 Supplement 1): AB16. #notes#.	Pooled analysis of relevant RCTs
939	Chipps B.E., McDonald M., Garin M. (2018//) Baseline characteristics associated with quartiles of reslizumab effect: pooled analysis of two phase 3 studies. Journal of Allergy and Clinical Immunology 141 (2 Supplement 1): AB16. #notes#.	Pooled analysis of relevant RCTs
940	Hanania N.A., Rosen K., Griffin N.M., Trzaskoma B.L., Haselkorn T., Chipps B.E., Casale T.B. (2018//) Response to omalizumab observed over wide range of blood eosinophil levels. Journal of Allergy and Clinical Immunology 141 (2 Supplement 1): AB15. #notes#.	Pooled analysis of relevant RCTs
944	Park H.-S., Lee S.H., Werkstrom V., Wu Y., Zangrilli J., Gopalan G. (2018//) Benralizumab reduces exacerbations and improves lung function in patients from republic of Korea with severe, uncontrolled asthma: Subgroup analysis of the SIROCCO Trial. Journal of Allergy and Clinical Immunology 141 (2 Supplement 1): AB14. #notes#.	Subgroup analysis not of interest
947	DuBuske L., Newbold P., Wu Y., Trudo F., Gopalan G. (2018//) Seasonal variability of exacerbations in patients with severe, uncontrolled eosinophilic asthma and clinical benefits of benralizumab: Pooled analysis of the SIROCCO and CALIMA Trials. Journal of Allergy and Clinical Immunology 141 (2 Supplement 1): AB12. #notes#.	Pooled analysis of relevant RCTs
948	Maspero J., Harrison T., Werkstrom V., Wu Y., Gopalan G., Zangrilli J. (2018//) Clinical efficacy of benralizumab in patients with severe, uncontrolled eosinophilic asthma and nasal polyposis: Pooled Analysis of the SIROCCO and CALIMA Trials. Journal of Allergy and Clinical Immunology 141 (2 Supplement 1): AB12. #notes#.	Subgroup analysis not of interest
955	Carr W.W., McDonald M., Meizlik P. (2018//) Reslizumab improves FVC and FEF25%-75% in severe eosinophilic asthma: Results from a pooled analysis. Journal of Allergy and Clinical Immunology 141 (2 Supplement 1): AB195. #notes#.	Pooled analysis of relevant RCTs
959	Castro M., Swanson B.N., Jayawardena S., Hamilton J.D., Amin N., Pirozzi G., Graham N.M.H., Teper A. (2018//) Exacerbation risk and type 2 inflammation in placebo patients during a phase 2b study of dupilumab in patients with uncontrolled persistent asthma. Journal of Allergy and Clinical Immunology 141 (2 Supplement 1): AB112. #notes#.	Subgroup analysis not of interest
960	Korenblat P.E., McDonald M., Garin M. (2018//) Improvements in individual asthma control questionnaire (ACQ-5) questions with reslizumab in patients with inadequately controlled asthma and elevated blood eosinophils: Pooled analysis of two phase 3 trials. Journal of Allergy and Clinical Immunology 141 (2 Supplement 1): AB17. #notes#.	Pooled analysis of relevant RCTs

961	Manning E., Garin M., Jiang B., Sun S.X. (2018//) Impact of reslizumab on duration of exacerbations in patients with severe eosinophilic asthma Michael. Journal of Allergy and Clinical Immunology 141 (2 Supplement 1): AB17. #notes#.	Pooled analysis of relevant RCTs
963	Castro M, Corren J, Pavord ID, Maspero JF, Wenzel SE, Rabe KF, Busse WW, Ford LB, Sher L, FitzGerald J, Katelaris C, Tohda Y, Zhang B, Staudinger H, Pirozzi G, Amin N, Ruddy M, Akinlade B, Khan A, Chao J, Martincova R, Graham NM, Teper A (2018//) A randomized, controlled phase 3 study, liberty asthma quest, evaluating the efficacy and safety of dupilumab in uncontrolled moderate-to-severe asthma. #journal# 197 (MeetingAbstracts): #pages#. #notes#.	Duplicate
964	Corren J, Castro M, Guillonneau S, Chao J, Amin N, Pirozzi G, Graham NM, Teper A, Khan A (2018//) Dupilumab produces rapid and sustained improvements in asthma-related symptoms in patients with uncontrolled, moderate-to-severe asthma from the liberty asthma quest study. #journal# 197 (MeetingAbstracts): #pages#. #notes#.	Duplicate
965	Castro M, Busse WW, Zhang B, Maroni J, Rowe P, Amin N, Pirozzi G, Graham NM, Teper A (2018//) Dupilumab treatment produces rapid and sustained improvements in FEV1 in patients with uncontrolled, moderate-to-severe asthma from the LIBERTY ASTHMA QUEST study. #journal# 197 (MeetingAbstracts): #pages#. #notes#.	Duplicate
966	(2018//) Clinical efficacy of benralizumab in patients with severe, uncontrolled eosinophilic asthma and nasal polyposis: pooled Analysis of the SIROCCO and CALIMA Trials. Clinical efficacy of benralizumab in patients with severe, uncontrolled eosinophilic asthma and nasal polyposis: pooled Analysis of the SIROCCO and CALIMA Trials Conference: 2018 American Academy of Allergy, Asthma and Immunology, AAAAI and World Allergy Organization, WAO Joint Congress. United States. 141 (2 Supplement 1): AB12. #notes#.	Duplicate
967	(2018//) Semi-mechanistic pharmacokinetic/pharmacodynamic (PK/PD) modeling of dupilumab on pre-bronchodilator forced expiratory volume in 1 second (FEV1) in uncontrolled moderate-to-severe asthma. Semi-mechanistic pharmacokinetic/pharmacodynamic (PK/PD) modeling of dupilumab on pre-bronchodilator forced expiratory volume in 1 second (FEV1) in uncontrolled moderate-to-severe asthma Conference: 9th American Conference on Pharmacometrics, ACoP 2018. United States. 45 (Supplement 1): S69. #notes#.	Duplicate
968	(2018//) Dupilumab shows rapid and sustained suppression of inflammatory biomarkers in asthma patients in liberty asthma quest. Dupilumab shows rapid and sustained suppression of inflammatory biomarkers in asthma patients in liberty asthma quest 52 (#issue#): #pages#. #notes#.	Duplicate
969	(2018//) Dupilumab reduces exacerbations and improves lung function in uncontrolled, moderate-tosevere asthma patients regardless of prior exacerbation history in the phase 3 liberty asthma quest study. Dupilumab reduces exacerbations and improves lung function in uncontrolled, moderate-tosevere asthma patients regardless of prior exacerbation history in the phase 3 liberty asthma quest study 73 (#issue#): A121. #notes#.	Duplicate
970	Niven RM, Simmonds MR, Cangelosi MJ, Tilden DP, Cottrell S, Shargill NS (2018//) Indirect comparison of bronchial thermoplasty versus omalizumab for uncontrolled severe asthma. #journal# 55 (4): 443. #notes#.	On topic SLR/MA/NMA
971	Busse WW, Bleecker ER, Ferguson GT, Barker P, Sproule S, Olsson RF, Martin UJ, Goldman M, Yanez A, Fernandez M, Tolcachier A, Belloni J, Taborda J, De Salvo M, Maspero J, Victorio C, Navarta MC, Grilli M, Rodriguez P, Otaola M, Cambursano V, Malamud P, Stok A, Arce G, Roza O, Scherbovsky F, Elias P, Saez MS, Peters M, Phillips M, Upham J, Gibson P, Thien F, Douglass J, Thomas P,	Duplicate

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972	Bleecker ER, Wechsler ME, FitzGerald JM, Menzies-Gow A, Wu Y, Hirsch I, Goldman M, Newbold P, Zangrilli JG (2018//) Baseline patient factors impact on the clinical efficacy of benralizumab for severe asthma. #journal# 52 (4): #pages#. #notes#.	Duplicate
974	Shrimanker R, Pavord ID, Yancey S, Heaney LG, Green RH, Bradding P, Hargadon B, Brightling CE, Wardlaw AJ, Haldar P (2018//) Exacerbations of severe asthma in patients treated with mepolizumab. #journal# 52 (6): #pages#. #notes#.	Duplicate
976	EUCTR2017-003289-29-PL (2018//) Evaluation of SAR440340/REGN3500 and as Combination Therapy with dupilumab in Moderate-to-Severe Asthma Patients. A Randomized, Double-blind, Placebo-controlled, Parallel-group, 12-week Proof-of-Concept (PoC) Study to Assess the Efficacy, Safety, and Tolerability of SAR440340/REGN3500 and the Coadministration of SAR440340 and Dupilumab in Patients with Moderate-to-severe Asthma who are not well Controlled on Inhaled Corticosteroid (ICS) plus Long-acting [latin sharp s]2 Adrenergic Agonist (LABA) Therapy #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
981	NCT03727971 (2018//) Pregnancy Rate, Asthma, Infertility, Omalizumab. Use of Omalizumab Will Increase the Pregnancy Rate, Proof of Concept Study, Where Women With Asthma and Infertility Will be Treated Three Times With Weight and IgE Balanced Dosis at the First Day of Their Period Bleeding #volume# (#issue#): #pages#. #notes#.	Intervention/Comparator
985	(2018//) Dupilumab reduces risk of severe exacerbations and improves fev1 regardless of baseline disease severity in patients with uncontrolled, moderate-to-severe asthma: data from the phase 3 liberty asthma quest study. Dupilumab reduces risk of severe exacerbations and improves fev1 regardless of baseline disease severity in patients with uncontrolled, moderate-to-severe asthma: data from the phase 3 liberty asthma quest study 73 (#issue#): A48. #notes#.	Duplicate
986	NCT03406078 (2018//) Study to Evaluate the Efficacy and Safety of Tezepelumab in Reducing Oral Corticosteroid Use in Adults With Oral Corticosteroid Dependent Asthma. A Multicentre, Randomized, Double-Blind, Placebo Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Tezepelumab in Reducing Oral Corticosteroid Use in Adults With Oral Corticosteroid Dependent Asthma (SOURCE) #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
987	NCT03387852 (2018//) Evaluation of SAR440340 and as Combination Therapy With Dupilumab in Moderate-to-Severe Asthma Patients. A Randomized, Double-blind, Placebo-controlled, Parallel-group, 12-week Proof-of-Concept (PoC) Study to Assess the Efficacy, Safety, and Tolerability of SAR440340 and the Coadministration of SAR440340 and Dupilumab in Patients With Moderate-to-severe Asthma Who Are Not Well Controlled on Inhaled Corticosteroid (ICS) Plus Long-acting [beta]2 Adrenergic Agonist (LABA) Therapy #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
989	NCT03562195 (2018//) A Safety and Efficacy Study of Mepolizumab in Subjects With Severe Asthma. A Randomized, Double Blind, Parallel Group Study of the Efficacy and Safety of Mepolizumab as Adjunctive Therapy in Patients With	Relevant clinical trial records

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990	NCT03688074 (2018//) Study to Evaluate Tezepelumab on Airway Inflammation in Adults With Uncontrolled Asthma (CASCADE). A Phase 2, Randomized, Double-blind, Parallel Group, Placebo Controlled Study to Evaluate the Effect of Tezepelumab on Airway Inflammation in Adults With Inadequately Controlled Asthma on Inhaled Corticosteroids and at Least One Additional Asthma Controller (CASCADE) #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
991	NCT03706079 (2018//) Extension Study to Evaluate the Safety and Tolerability of Tezepelumab in Adults and Adolescents With Severe, Uncontrolled Asthma. A Multicentre, Double-blind, Randomized, Placebo Controlled, Parallel Group, Phase 3, Safety Extension Study to Evaluate the Safety and Tolerability of Tezepelumab in Adults and Adolescents With Severe Uncontrolled Asthma (DESTINATION) #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
992	NCT03694158 (2018//) Effect of IL-4R[alpha]R576 Polymorphism on Response to Dupilumab in Children With Asthma. Effect of IL-4R[alpha]R576 Polymorphism on Response to Dupilumab in Children With Asthma #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
993	NCT03610685 (2018//) Inflammation Following Mepolizumab and Oral Corticosteroids in Asthma. Persistence of Inflammation and Study of T2 Pathways Following Inhibition of InterLeukin-5 With Mepolizumab in Severe Eosinophilic Asthma #volume# (#issue#): #pages#. #notes#.	Intervention/Comparator
994	NCT03782532 (2018//) Efficacy and Safety Study of Dupilumab in Patients With Persistent Asthma. A Randomized, Double Blind, Placebo-controlled, Parallel-group Phase 3 Study to Evaluate the Efficacy and Safety of Dupilumab in Patients With Persistent Asthma #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
996	Sehmi R, Lim HF, Mukherjee M, Huang C, Radford K, Newbold P, Boulet LP, Dorscheid D, Martin JG, Nair P (2018//) Benralizumab attenuates airway eosinophilia in prednisone-dependent asthma. #journal# 141 (4): 1529. #notes#.	Population
997	(2018//) Dupilumab efficacy in asthma patients with comorbid chronic rhinosinusitis or nasal polyposis (CRS/NP) in LIBERTY ASTHMA QUEST. Dupilumab efficacy in asthma patients with comorbid chronic rhinosinusitis or nasal polyposis (CRS/NP) in LIBERTY ASTHMA QUEST 52 (#issue#): #pages#. #notes#.	Duplicate
998	(2018//) Dupilumab improves asthma-related patient reported outcomes in asthma patients with chronic rhinosinusitis or nasal polyposis (CRS/NP) in liberty asthma quest. Dupilumab improves asthma-related patient reported outcomes in asthma patients with chronic rhinosinusitis or nasal polyposis (CRS/NP) in liberty asthma quest 52 (#issue#): #pages#. #notes#.	Duplicate
999	(2018//) Effects of Reslizumab on Asthma Outcomes in a Subgroup of Eosinophilic Asthma Patients with Self-Reported Chronic Rhinosinusitis with Nasal Polyps. Effects of Reslizumab on Asthma Outcomes in a Subgroup of Eosinophilic Asthma Patients with Self-Reported Chronic Rhinosinusitis with Nasal Polyps #volume# (#issue#): #pages#. #notes#.	Duplicate
1001	(2018//) Mepolizumab for severe eosinophilic asthma: a comparison of efficacy in children, adolescents, and adults. Mepolizumab for severe eosinophilic asthma: a comparison of efficacy in children, adolescents, and adults 52 (#issue#): #pages#. #notes#.	Duplicate
1002	(2018//) Exposure-response analysis of tezepelumab in patients with severe asthma to guide phase 3 dose selection. Exposure-response analysis of	Duplicate

	tezepelumab in patients with severe asthma to guide phase 3 dose selection 52 (#issue#): #pages#. #notes#.	
1003	(2018//) Consistent efficacy across endpoints with reslizumab despite short term variability in blood eosinophil levels. Consistent efficacy across endpoints with reslizumab despite short term variability in blood eosinophil levels 52 (#issue#): #pages#. #notes#.	Duplicate
1004	(2018//) Benralizumab efficacy in patients with uncontrolled eosinophilic asthma by age at diagnosis. Benralizumab efficacy in patients with uncontrolled eosinophilic asthma by age at diagnosis 52 (#issue#): #pages#. #notes#.	Duplicate
1005	(2018//) Intravenous (IV) reslizumab efficacy does not differ by blood eosinophil lowering to levels above or below 50 cells/[mu]l. Intravenous (IV) reslizumab efficacy does not differ by blood eosinophil lowering to levels above or below 50 cells/[mu]l 52 (#issue#): #pages#. #notes#.	Duplicate
1006	Chanez P, Adir Y, Castro M, Pahus L, McDonald M, Hickey L, Garin M (2018//) Intravenous (IV) reslizumab improves asthma control, symptoms, and quality of life in patients with historically elevated blood eosinophils. #journal# 52 (#issue#): #pages#. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1007	(2018//) Demographics, clinical characteristics, and response to benralizumab treatment for patients with severe, eosinophilic asthma and fixed airflow obstruction. Demographics, clinical characteristics, and response to benralizumab treatment for patients with severe, eosinophilic asthma and fixed airflow obstruction Conference: American Thoracic Society International Conference, ATS 2018. United States. 197 (MeetingAbstracts): #pages#. #notes#.	Duplicate
1008	(2018//) Decreases in blood eosinophil levels correlate with lung function improvement with reslizumab treatment. Decreases in blood eosinophil levels correlate with lung function improvement with reslizumab treatment Conference: American Thoracic Society International Conference, ATS 2018. United States. 197 (MeetingAbstracts): #pages#. #notes#.	Duplicate
1009	(2018//) Patient-reported activity impairment, stress, and tiredness improvement in patients with severe, uncontrolled asthma with eosinophilic inflammation: pooled results from two phase III trials of benralizumab. Patient-reported activity impairment, stress, and tiredness improvement in patients with severe, uncontrolled asthma with eosinophilic inflammation: pooled results from two phase III trials of benralizumab Conference: 59. Kongress der Deutschen Gesellschaft fur Pneumologie und Beatmungsmedizin e.V.. Germany. 72 (Supplement 1): #pages#. #notes#.	Duplicate
1010	(2018//) Effects of immunoglobin e concentration, eosinophil concentration, and atopy status on benralizumab efficacy in asthma. Effects of immunoglobin e concentration, eosinophil concentration, and atopy status on benralizumab efficacy in asthma Conference: 59. Kongress der Deutschen Gesellschaft fur Pneumologie und Beatmungsmedizin e.V.. Germany. 72 (Supplement 1): #pages#. #notes#.	Duplicate
1011	(2018//) Efficacy of benralizumab for patients with severe, uncontrolled atopic asthma by serum immunoglobulin e concentrations. Efficacy of benralizumab for patients with severe, uncontrolled atopic asthma by serum immunoglobulin e concentrations Conference: 59. Kongress der Deutschen Gesellschaft fur Pneumologie und Beatmungsmedizin e.V.. Germany. 72 (Supplement 1): #pages#. #notes#.	Duplicate
1012	(2018//) Asthma symptom improvements with benralizumab are associated with improvements in activity function and quality of life for patients with severe, uncontrolled asthma. Asthma symptom improvements with	Pooled analysis of relevant RCTs

	benralizumab are associated with improvements in activity function and quality of life for patients with severe, uncontrolled asthma Conference: 59. Kongress der Deutschen Gesellschaft fur Pneumologie und Beatmungsmedizin e.V.. Germany. 72 (Supplement 1): #pages#. #notes#.	
1013	(2018//) Fractional exhaled nitric oxide and the peripheral blood eosinophil count as biomarkers of the response to mepolizumab in patients with severe eosinophilic asthma. Fractional exhaled nitric oxide and the peripheral blood eosinophil count as biomarkers of the response to mepolizumab in patients with severe eosinophilic asthma Conference: American Thoracic Society International Conference, ATS 2018. United States. 197 (MeetingAbstracts): #pages#. #notes#.	Duplicate
1014	(2018//) Influence of key clinical baseline factors on benralizumab efficacy for patients with severe, uncontrolled asthma. Influence of key clinical baseline factors on benralizumab efficacy for patients with severe, uncontrolled asthma Conference: American Thoracic Society International Conference, ATS 2018. United States. 197 (MeetingAbstracts): #pages#. #notes#.	Duplicate
1015	(2018//) Reslizumab high-responder and super-responder asthma patients. Reslizumab high-responder and super-responder asthma patients Conference: American Thoracic Society International Conference, ATS 2018. United States. 197 (MeetingAbstracts): #pages#. #notes#.	Subgroup analysis not of interest
1017	(2018//) Baseline patient factors impact on the clinical efficacy of benralizumab for severe asthma. Baseline patient factors impact on the clinical efficacy of benralizumab for severe asthma 52 (4): #pages#. #notes#.	Duplicate
1019	(2018//) IMPROVEMENTS WITH RESLIZUMAB TREATMENT IN PATIENT-REPORTED SLEEP QUALITY IN PATIENTS WITH INADEQUATELY CONTROLLED EOSINOPHILIC ASTHMA. IMPROVEMENTS WITH RESLIZUMAB TREATMENT IN PATIENT-REPORTED SLEEP QUALITY IN PATIENTS WITH INADEQUATELY CONTROLLED EOSINOPHILIC ASTHMA Conference: 2018 Annual Scientific Meeting of the American College of Allergy Asthma and Immunology. United States. 121 (5 Supplement): S43. #notes#.	Duplicate
1021	Rabe KF, Nair PK, Brusselle GG, Maspero JF, Castro M, Zhu H, Staudinger H, Pirozzi G, Antoni C, Amin N, Ruddy M, Akinlade B, Khan A, Chao J, Graham NM, Teper A (2018//) Dupilumab in patients with corticosteroid-dependent severe asthma: efficacy and safety results from the randomized, double-blind, placebo-controlled phase 3 liberty asthma venture study. #journal# 197 (MeetingAbstracts): #pages#. #notes#.	Duplicate
1022	Li J, Kang J, Wang C, Yang J, Lin Z, Wang S, Humphries M, Kottakis I, Fogel R, Zhong N (2018//) Serum ige levels as predictor for treatment outcomes in chinese patients with moderate or severe allergic asthma treated with omalizumab. #journal# 197 (MeetingAbstracts): #pages#. #notes#.	Duplicate
1023	Wang C, Li J, Kang J, Yang J, Lin Z, Wang S, Humphries M, Kottakis I, Fogel R, Zhong N (2018//) Clinical efficacy of omalizumab, as measured by patient-reported outcomes, in chinese patients with moderate or severe allergic asthma. #journal# 197 (MeetingAbstracts): #pages#. #notes#.	Duplicate
1024	Pahus L, Bourdin A, McDonald M, Meizlik P, Chanez P (2018//) Up to four years of longitudinal follow-up for patients with severe eosinophilic asthma receiving reslizumab. #journal# 197 (MeetingAbstracts): #pages#. #notes#.	Duplicate
1026	Murphy KR, McDonald M, Garin MC (2018//) Improvements in exacerbation rate and lung function with weight-based intravenous reslizumab dosing in patients with baseline high body weight. #journal# 197 (MeetingAbstracts): #pages#. #notes#.	Subgroup analysis not of interest

1030	Bardford E, Nelsen L, Bratton D, Albers F, Taille C, Magnan A (2018//) Efficacy of mepolizumab in patients with severe eosinophilic asthma who had previously received omalizumab treatment. #journal# 72 (#issue#): #pages#. #notes#.	Duplicate
1031	Ortega H, Albers F, Llanos JP, Bardford E, Price G, Pouliquen I, Castro M (2018//) Impact of weight on the efficacy of mepolizumab in patients with severe eosinophilic asthma. #journal# 72 (#issue#): #pages#. #notes#.	Subgroup analysis not of interest
1032	Roskos L, Wang B, Chia YL, Yu B, Barker P, Goldman M (2018//) Relationship between benralizumab exposure and asthma exacerbation rate for patients with severe asthma. #journal# 72 (#issue#): #pages#. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1033	Roskos L, Wang B, Yan L, Yu B, Barker P, Goldman M (2018//) Longitudinal modeling of prebronchodilator FEV1 response to benralizumab for patients with severe asthma. #journal# 72 (#issue#): #pages#. #notes#.	Duplicate
1034	Lugogo N, Kline JN, Hirsch I, Goldman M, Zangrilli JG, Trudo F (2018//) Benralizumab improves morning peak expiratory flow while reducing oral corticosteroid dosages for patients with severe, uncontrolled asthma in the zonda phase III trial. #journal# 197 (MeetingAbstracts): #pages#. #notes#.	Duplicate
1035	(2018//) Benralizumab treatment produces rapid changes in morning peak expiratory flow in patients with severe, uncontrolled eosinophilic asthma. Benralizumab treatment produces rapid changes in morning peak expiratory flow in patients with severe, uncontrolled eosinophilic asthma Conference: 2018 American Academy of Allergy, Asthma and Immunology, AAAAI and World Allergy Organization, WAO Joint Congress. United States. 141 (2 Supplement 1): AB15. #notes#.	Duplicate
1036	(2018//) Seasonal variability of exacerbations in patients with severe, uncontrolled eosinophilic asthma and clinical benefits of benralizumab: pooled analysis of the SIROCCO and CALIMA Trials. Seasonal variability of exacerbations in patients with severe, uncontrolled eosinophilic asthma and clinical benefits of benralizumab: pooled analysis of the SIROCCO and CALIMA Trials Conference: 2018 American Academy of Allergy, Asthma and Immunology, AAAAI and World Allergy Organization, WAO Joint Congress. United States. 141 (2 Supplement 1): AB12. #notes#.	Duplicate
1037	(2018//) Improvements in individual asthma control questionnaire (ACQ-5) questions with reslizumab in patients with inadequately controlled asthma and elevated blood eosinophils: pooled analysis of two phase 3 trials. Improvements in individual asthma control questionnaire (ACQ-5) questions with reslizumab in patients with inadequately controlled asthma and elevated blood eosinophils: pooled analysis of two phase 3 trials Conference: 2018 American Academy of Allergy, Asthma and Immunology, AAAAI and World Allergy Organization, WAO Joint Congress. United States. 141 (2 Supplement 1): AB17. #notes#.	Duplicate
1038	(2018//) Rapid and Consistent Improvements in Morning PEF in Patients with Severe Eosinophilic Asthma Treated with Mepolizumab. Rapid and Consistent Improvements in Morning PEF in Patients with Severe Eosinophilic Asthma Treated with Mepolizumab #volume# (#issue#): 1. #notes#.	Duplicate
1043	Bondar, Anna, Carr, Megan (2017//) Reslizumab (Cinqair) for Eosinophilic Asthma.. American family physician 96 (10): 671. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1044	Condreay, Lynn, Chiano, Mathias, Ortega, Hector, Buchan, Natalie, Harris, Elizabeth, Bleecker, Eugene R, Thompson, Philip J, Humbert, Marc, Gibson, Peter, Yancey, Steven, Ghosh, Soumitra (2017//) No genetic association	Study design (non-RCT, opinion, commentary, single-arm, etc)

	detected with mepolizumab efficacy in severe asthma.. Respiratory medicine 132 (#issue#): 178. #notes#.	
1078	Gouder, Caroline, Asciak, Rachelle, Montefort, Stephen (2017//) Sex differences in the efficacy, safety, and tolerability of omalizumab after 1 year in Maltese patients with asthma.. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 118 (4): 513. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1094	FitzGerald J.M., Lemiere C., Lougheed M.D., Ducharme F.M., Dell S.D., Ramsey C., Yang M.C.L., Cote A., Watson W., Olivenstein R., Van Dam A., Villa-Roel C., Grad R. (2017//) Recognition and management of severe asthma: A Canadian Thoracic Society position statement. Canadian Journal of Respiratory, Critical Care, and Sleep Medicine 1 (4): 199. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1096	Attaway A., Ayache M., Velani S., McKell J. (2017//) Insights into asthma therapies, cardiovascular effects, and mechanisms from recent clinical trials. American Journal of Respiratory and Critical Care Medicine 196 (7): 920. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1097	Albers F.C., Price R.G., Smith S.G., Yancey S.W. (2017//) Mepolizumab efficacy in patients with severe eosinophilic asthma receiving different controller therapies. Journal of Allergy and Clinical Immunology 140 (5): 1464. #notes#.	Pooled analysis of relevant RCTs
1100	Sutherland M.F., Le Portelli E., Collins A.L., Rahman M.A., McDonald C.F. (2017//) Patients with thunderstorm asthma or severe asthma in melbourne: A comparison. Medical Journal of Australia 207 (10): 434. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1101	Murphy K., Jacobs J., Bjermer L., Fahrenholz J.M., Shalit Y., Garin M., Zangrilli J., Castro M. (2017//) Long-term Safety and Efficacy of Reslizumab in Patients with Eosinophilic Asthma. Journal of Allergy and Clinical Immunology: In Practice 5 (6): 1572. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1109	Esquivel A., Busse W.W., Calatroni A., Togias A.G., Grindle K.G., Bochkov Y.A., Gruchalla R.S., Kattan M., Kercsmar C.M., Hershey G.K., Kim H., Lebeau P., Liu A.H., Szefler S.J., Teach S.J., West J.B., Wildfire J., Pongracic J.A., Gern J.E. (2017//) Effects of Omalizumab on Rhinovirus Infections, Illnesses, and exacerbations of asthma. American Journal of Respiratory and Critical Care Medicine 196 (8): 985. #notes#.	Incomplete/Insufficient/Partial data
1117	Iribarren C., Rothman K.J., Bradley M.S., Carrigan G., Eisner M.D., Chen H. (2017//) Cardiovascular and cerebrovascular events among patients receiving omalizumab: Pooled analysis of patient-level data from 25 randomized, double-blind, placebo-controlled clinical trials. Journal of Allergy and Clinical Immunology 139 (5): 1678. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1123	Fuhlbrigge A.L., Bengtsson T., Peterson S., Jauhiainen A., Eriksson G., Da Silva C.A., Johnson A., Sethi T., Locantore N., Tal-Singer R., Fageras M. (2017//) A novel endpoint for exacerbations in asthma to accelerate clinical development: a post-hoc analysis of randomised controlled trials. The Lancet Respiratory Medicine 5 (7): 577. #notes#.	Intervention/Comparator
1124	Nelsen L.M., Vernon M., Ortega H., Cockle S.M., Yancey S.W., Brusselle G., Albers F.C., Jones P.W. (2017//) Evaluation of the psychometric properties of the St George's Respiratory Questionnaire in patients with severe asthma. Respiratory Medicine 128 (#issue#): 42. #notes#.	Pooled analysis of relevant RCTs
1125	Cabon Y., Molinari N., Marin G., Vachier I., Gamez A.S., Chanez P., Bourdin A. (2017//) Comparison of anti-interleukin-5 therapies in patients with severe asthma: global and indirect meta-analyses of randomized placebo-controlled trials. Clinical and Experimental Allergy 47 (1): 129. #notes#.	On topic SLR/MA/NMA

1128	Shimoda T., Odajima H., Okamasa A., Kawase M., Komatsubara M., Mayer B., Yancey S., Ortega H. (2017//) Efficacy and safety of mepolizumab in Japanese patients with severe eosinophilic asthma. Allergology International 66 (3): 445. #notes#.	Subgroup analysis not of interest
1129	Corren J., Kavati A., Ortiz B., Colby J.A., Ruiz K., Maiese B.A., Cadarette S.M., Panettieri R.A. (2017//) Efficacy and safety of omalizumab in children and adolescents with moderate-to-severe asthma: A systematic literature review. Allergy and Asthma Proceedings 38 (4): 250. #notes#.	On topic SLR/MA/NMA
1134	Cockle S.M., Stynes G., Gunsoy N.B., Parks D., Alfonso-Cristancho R., Wex J., Bradford E.S., Albers F.C., Willson J. (2017//) Comparative effectiveness of mepolizumab and omalizumab in severe asthma: An indirect treatment comparison. Respiratory Medicine 123 (#issue#): 140. #notes#.	On topic SLR/MA/NMA
1138	Farne H.A., Wilson A., Powell C., Bax L., Milan S.J. (2017//) Anti-IL5 therapies for asthma. Cochrane Database of Systematic Reviews 2017 (9): CD010834. #notes#.	On topic SLR/MA/NMA
1139	Brusselle G., Germinaro M., Weiss S., Zangrilli J. (2017//) Reslizumab in patients with inadequately controlled late-onset asthma and elevated blood eosinophils. Pulmonary Pharmacology and Therapeutics 43 (#issue#): 39. #notes#.	Pooled analysis of relevant RCTs
1147	Ledford D., Busse W., Trzaskoma B., Omachi T.A., Rosen K., Chipps B.E., Luskin A.T., Solari P.G. (2017//) A randomized multicenter study evaluating Xolair persistence of response after long-term therapy. Journal of Allergy and Clinical Immunology 140 (1): 162. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1149	Brusselle G., Canvin J., Weiss S., Sun S.X., Buhl R. (2017//) Stratification of eosinophilic asthma patients treated with reslizumab and GINA step 4 or 5 therapy. ERJ Open Research 3 (3): 00004-2017. #notes#.	Pooled analysis of relevant RCTs
1151	Yancey S.W., Ortega H.G., Keene O.N., Mayer B., Gunsoy N.B., Brightling C.E., Bleecker E.R., Haldar P., Pavord I.D. (2017//) Meta-analysis of asthma-related hospitalization in mepolizumab studies of severe eosinophilic asthma. Journal of Allergy and Clinical Immunology 139 (4): 1167. #notes#.	On topic SLR/MA/NMA
1156	Li J., Wang F., Lin C., Du J., Xiao B., Du C., Sun J. (2017//) The efficacy and safety of reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: A systematic review and meta-analysis. Journal of Asthma 54 (3): 300. #notes#.	On topic SLR/MA/NMA
1162	Odajima H., Ebisawa M., Nagakura T., Fujisawa T., Akasawa A., Ito K., Doi S., Yamaguchi K., Katsunuma T., Kurihara K., Teramoto T., Sugai K., Nambu M., Hoshioka A., Yoshihara S., Sato N., Seko N., Nishima S. (2017//) Long-term safety, efficacy, pharmacokinetics and pharmacodynamics of omalizumab in children with severe uncontrolled asthma. Allergology International 66 (1): 106. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1164	Chauhan A., Garin M., Sun S. (2017//) Efficacy of reslizumab in adults with severe eosinophilic asthma with >=3 exacerbations in the previous year: Analyses at weeks 16 and 52 of two placebo-controlled phase 3 trials. European Respiratory Journal 50 (Supplement 61): #pages#. #notes#.	Pooled analysis of relevant RCTs
1165	Nair P., Mukherjee M., Fang Lim H., Huang C., Radford K., Boulet L.-P., Dorscheid D., Martin J.G., Sehmi R. (2017//) Benralizumab attenuates airway eosinophilopoietic processes in prednisone-dependent asthma. European Respiratory Journal 50 (Supplement 61): #pages#. #notes#.	Subgroup analysis not of interest
1166	Katial R., Joish V.N., Amin N., Rowe P., Maroni J., Pirozzi G., Graham N.M.H., Guillonneau S., Teper A., Eckert L., Taniou C. (2017//) Dupilumab improves patient-reported outcomes in uncontrolled persistent asthma patients with	Subgroup analysis not of interest

	ongoing allergic rhinitis. European Respiratory Journal 50 (Supplement 61): #pages#. #notes#.	
1167	Weinstein S., Staudinger H., Guillonneau S., Taniou C., Eckert L., Joish V., Maroni J., Rowe P., Amin N., Pirozzi G., Graham N., Teper A. (2017//) Dupilumab improves lung function and reduces severe exacerbations in uncontrolled persistent asthma patients with ongoing allergic rhinitis. European Respiratory Journal 50 (Supplement 61): #pages#. #notes#.	Subgroup analysis not of interest
1169	Roseti S., Corren J., Parnes J., Mo M., Griffiths J., Wang L., Van Der Merwe R. (2017//) Late Breaking Abstract-Efficacy and safety of tezepelumab in adults with severe asthma: A randomized phase 2 study. European Respiratory Journal 50 (Supplement 61): #pages#. #notes#.	Duplicate
1171	Wang B., Chia Y.L., Yu B., Barker P., Goldman M., Roskos L. (2017//) Relationship between benralizumab exposure and asthma exacerbation rate for patients with severe asthma. European Respiratory Journal 50 (Supplement 61): #pages#. #notes#.	Duplicate
1173	Brannman L., Ouwens M., Golam S.M. (2017//) Exacerbation utilities and durations by type: Estimates from Phase III benralizumab studies. European Respiratory Journal 50 (Supplement 61): #pages#. #notes#.	Pooled analysis of relevant RCTs
1174	Chanez P., Garin M., McDonald M., Humbert M. (2017//) Reslizumab reduces severe exacerbations associated with emergency department visit or hospitalization and improves measures of lung function in patients on maintenance oral corticosteroids (OCS) at baseline. European Respiratory Journal 50 (Supplement 61): #pages#. #notes#.	Pooled analysis of relevant RCTs
1175	Virchow J.C., Garin M., McDonald M., Buhl R. (2017//) Clinically meaningful FEV1 response with reslizumab achieved early and sustained over 52 weeks. European Respiratory Journal 50 (Supplement 61): #pages#. #notes#.	Pooled analysis of relevant RCTs
1177	Fang L., Roth M., Sun Q., Savic S., Tamm M., Stolz D. (2017//) Late Breaking Abstract-Bronchial Thermoplasty restores constitutive high PRMT1 expression in asthmatic airways. European Respiratory Journal 50 (Supplement 61): #pages#. #notes#.	Duplicate
1178	Bjermer L., Garin M., Sun S.X. (2017//) Clinically meaningful improvements with reslizumab in patient-reported outcomes and lung function in a sub-population defined by the EU indication with >=3 exacerbations. European Respiratory Journal 50 (Supplement 61): #pages#. #notes#.	Pooled analysis of relevant RCTs
1179	Casale T., Mesana L., Pacou M., Farge G., Sun S.X., Castro M. (2017//) Reslizumab vs benralizumab in patients with inadequately controlled asthma: A Bayesian network meta-analysis. European Respiratory Journal 50 (Supplement 61): #pages#. #notes#.	Incomplete/Insufficient/Partial data
1180	Fitz-Gerald J.M., Bleecker E.R., Menzies-Gow A., Zangrilli J.G., Metcalfe P., Hirsch I., Newbold P., Goldman M. (2017//) Characterizing responders to benralizumab for severe asthma: Pooled analysis of the SIROCCO and CALIMA studies. European Respiratory Journal 50 (Supplement 61): #pages#. #notes#.	Pooled analysis of relevant RCTs
1184	Shrimanker R., Hargaden B., Bradding P., Wardlaw A.J., Brightling C.E., Green R., Bafadhel M., Pavord I.D., Haldar P., Heaney L. (2017//) Characterisation of exacerbations of severe eosinophilic asthma (SEA) on mepolizumab compared to placebo. European Respiratory Journal 50 (Supplement 61): #pages#. #notes#.	Intervention/Comparator
1185	Chanez P., Garin M., McDonald M., Pahus L., Bourdin A. (2017//) A longitudinal follow-up of severe asthma patients receiving reslizumab. European Respiratory Journal 50 (Supplement 61): #pages#. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)

1186	Wang B., Yan L., Yu B., Barker P., Goldman M., Roskos L. (2017//) Longitudinal modeling of prebronchodilator FEV1 response to benralizumab for patients with severe asthma. European Respiratory Journal 50 (Supplement 61): #pages#. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1187	Shrimanker R., Hargaden B., Bradding P., Wardlaw A., Brightling C.E., Green R., Bafadhel M., Heaney L., Pavord I., Haldar P. (2017//) Mepolizumab and the response to oral prednisolone in patients with severe eosinophilic asthma. European Respiratory Journal 50 (Supplement 61): #pages#. #notes#.	Intervention/Comparator
1190	Nelsen L., S Bradford E., Bratton D.J., Albers F.C., Brusselle G. (2017//) Improvement in rhinosinusitis health related quality of life in patients with severe eosinophilic asthma. European Respiratory Journal 50 (Supplement 61): #pages#. #notes#.	Subgroup analysis not of interest
1191	Wechsler M., Garin M., McDonald M., Korn S. (2017//) Reslizumab for uncontrolled eosinophilic asthma in patients who experienced a single exacerbation in the previous year: Sub-analysis of two phase 3 trials. European Respiratory Journal 50 (Supplement 61): #pages#. #notes#.	Pooled analysis of relevant RCTs
1192	Castro M., Maspero J.F., Staudinger H., Jayawardena S., Maroni J., Rowe P., Amin N., Pirozzi G., Graham N.M.H., Teper A. (2017//) Dupilumab improves lung function and reduces severe exacerbations in uncontrolled persistent asthma patients with high and low reversibility. European Respiratory Journal 50 (Supplement 61): #pages#. #notes#.	Subgroup analysis not of interest
1197	Sharma R., Cheung A., Bolzani A., Barakat S., Sun S., Tarasova O., Druyts E., Fitzgerald M. (2017//) Comparative efficacy of reslizumab and mepolizumab for the treatment of severe eosinophilic asthma: A network meta-analysis. Canadian Journal of Respiratory Critical Care and Sleep Medicine 1 (3): 150. #notes#.	Incomplete/Insufficient/Partial data
1198	Pouliquen I., Austin D., Gunsoy N., Yancey S.W. (2017//) ENCORE: A weight-based exacerbation dose response analysis of mepolizumab in severe asthma with eosinophilic phenotype. Pneumologie 71 (Supplement 1): #pages#. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1206	Weinstein S.F., Katial R., Jayawardena S., Pirozzi G., Staudinger H., Eckert L., Joish V.N., Amin N., Maroni J., Rowe P., Graham N.M.H., Teper A. (2017//) Dupilumab improves sinonasal symptoms of perennial allergic rhinitis (PAR) in uncontrolled persistent asthma patients with comorbid par. Allergy and Asthma Proceedings 38 (3): 237. #notes#.	Subgroup analysis not of interest
1211	Park J.-W., Cho S.H., McDonald M., Garin M. (2017//) Reduction in exacerbations with reslizumab in korean patients with asthma and elevated blood eosinophils. Respirology 22 (Supplement 3): 169. #notes#.	Subgroup analysis not of interest
1212	Gopalan G., Xu X., O'Quinn S., Hirsch I. (2017//) Asthma symptom improvements with benralizumab are associated with improvements in activity functions and quality of life for patients with severe, uncontrolled asthma. Respirology 22 (Supplement 3): 168. #notes#.	Pooled analysis of relevant RCTs
1214	Gopalan G., O'Quinn S., Xu X., Hirsch I. (2017//) Patient-reported activity impairment, stress, and tiredness improvement in patients with severe, uncontrolled asthma with eosinophilic inflammation: Pooled results from two phase iii trials of benralizumab. Respirology 22 (Supplement 3): 8. #notes#.	Pooled analysis of relevant RCTs
1215	Gopalan G., Xu X., O'Quinn S., Hirsch I. (2017//) Impact of asthma control status on lung function and patient well-being assessments in patients with severe, uncontrolled asthma. Respirology 22 (Supplement 3): 160. #notes#.	Pooled analysis of relevant RCTs

1219	Marwaha H., Hartmann C.E.A., Mehta R.A., Gunsoy N.B., Albers F.C. (2017//) Therapeutic benefit of mepolizumab in the national institute of health and care excellence (NICE) sub-population-a post-HOC meta-analysis of phase IIB/III trials. Thorax 72 (Supplement 3): A90. #notes#.	On topic SLR/MA/NMA
1220	Gopalan G., Xu X., O'Quinn S., Hirsch I. (2017//) Asthma symptom improvements with benralizumab are associated with improvements in activity functions and quality of life for patients with severe, uncontrolled asthma: Results of pooled phase iii benralizumab studies. Thorax 72 (Supplement 3): A118. #notes#.	Pooled analysis of relevant RCTs
1222	Newbold P., Hirsch I., Trudo F., Goldman M. (2017//) Effects of immunoglobulin e concentration, eosinophil concentration, and atopy status on benralizumab efficacy in asthma. Annals of Allergy, Asthma and Immunology 119 (5 Supplement 1): S56. #notes#.	Pooled analysis of relevant RCTs
1223	Chipps B., Newbold P., Hirsch I., Trudo F., Goldman M. (2017//) Efficacy of benralizumab for patients with severe, uncontrolled atopic asthma by serum immunoglobulin e concentrations. Annals of Allergy, Asthma and Immunology 119 (5 Supplement 1): S56. #notes#.	Pooled analysis of relevant RCTs
1225	Panettieri R., McDonald M., Germinaro M. (2017//) Efficacy of reslizumab in eosinophilic asthma patients with low lung function. Annals of Allergy, Asthma and Immunology 119 (5 Supplement 1): S54. #notes#.	Subgroup analysis not of interest
1232	Carr W., McDonald M., Meizlik P. (2017//) Reslizumab improves spirometric lung age in patients with severe eosinophilic asthma. Annals of Allergy, Asthma and Immunology 119 (5 Supplement 1): S57. #notes#.	Pooled analysis of relevant RCTs
1242	Zhang L., Li M., Meng Z., Li Y., Davis J.D., Swanson B.N., Kanamaluru V., Lu Q. (2017//) Exposure-response analysis of dupilumab on forced expiratory volume in 1 Second (FEV1) in uncontrolled persistent asthma. Journal of Pharmacokinetics and Pharmacodynamics 44 (1 Supplement 1): S129. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1243	Zhang L., Li M., Meng Z., Li Y., Davis J.D., Swanson B.N., Kanamaluru V., Lu Q. (2017//) Population pharmacokinetic and pharmacodynamic modeling of thymus and activation-regulated chemokine (TARC) response to dupilumab in uncontrolled persistent asthma. Journal of Pharmacokinetics and Pharmacodynamics 44 (1 Supplement 1): S129. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1244	Yan L., Wang B., Yu B., Barker P., Goldman M., Roskos L. (2017//) Population modeling of pre-bronchodilator FEV1 response to benralizumab treatment in patients with severe asthma. Journal of Pharmacokinetics and Pharmacodynamics 44 (1 Supplement 1): S128. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1245	Chia Y.L., Wang B., Yu B., Barker P., Goldman M., Roskos L. (2017//) Exposure-response analysis of asthma exacerbation rate confirmed optimal 30 mg Q8W benralizumab dose for treatment of severe asthma. Journal of Pharmacokinetics and Pharmacodynamics 44 (1 Supplement 1): S58. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1246	Katelaris C.H., Maspero J.F., Jayawardena S., Rowe P., Maroni J., Pirozzi G., Amin N., Graham N.M.H., Mannent L., Teper A. (2017//) Dupilumab efficacy and effect on asthma control in patients with uncontrolled persistent asthma and comorbid chronic rhinosinusitis with or without nasal polyps. Internal Medicine Journal 47 (Supplement 5): 22. #notes#.	Subgroup analysis not of interest
1253	Prazma C.M., Idzko M., Bourdin A., Douglass J.A., Price R.G., Albers F., Yancey S.W. (2017//) Phenotypic characterization of severe atopic asthma patients treated with mepolizumab. Allergy: European Journal of Allergy and Clinical Immunology 72 (Supplement 103): 325. #notes#.	Pooled analysis of relevant RCTs

1255	Fabbri L.M., Bernstein J.A., Staudinger H., Maroni J., Rowe P., Jayawardena S., Joish V.N., Eckert L., Amin N., Akinlade B., Pirozzi G., Graham N.M., Teper A. (2017//) Dupilumab efficacy in severe asthma exacerbations by different baseline patient characteristics in patients with uncontrolled persistent asthma. Allergy: European Journal of Allergy and Clinical Immunology 72 (Supplement 103): 108. #notes#.	Subgroup analysis not of interest
1265	Busse W.W., Chipps B.E., Rosen K., Ortiz B., Haselkorn T., Trzaskoma B.L., Lanier B.Q., Szefler S.J. (2017//) Asthma exacerbations and lung function decline in a pooled analysis of adolescents and adults from randomized controlled trials of omalizumab. American Journal of Respiratory and Critical Care Medicine 195 (#issue#): #pages#. #notes#.	Pooled analysis of relevant RCTs
1267	McCauley K., Valladares R., LeBeau P., Tran H., Calatroni A., Boushey H.A., Gern J.E., Jackson D.J., Lynch S.V. (2017//) Distinct upper airway bacterial microbiota differentially relate to exacerbation and rhinovirus infection in pediatric asthmatics. American Journal of Respiratory and Critical Care Medicine 195 (#issue#): #pages#. #notes#.	Incomplete/Insufficient/Partial data
1269	Maspero J.F., Katelaris C., Jayawardena S., Rowe P., Maroni J., Pirozzi G., Amin N., Graham N.M.H., Mannent L., Teper A. (2017//) Dupilumab efficacy in uncontrolled persistent asthma patients with history of comorbid chronic rhinosinusitis with or without nasal polyps. American Journal of Respiratory and Critical Care Medicine 195 (#issue#): #pages#. #notes#.	Subgroup analysis not of interest
1273	Llanos-Ackert J.-P., Price R.G., Forshag M., Yancey S., Liu M.C. (2017//) Asthma control in patients with severe eosinophilic asthma treated with mepolizumab. American Journal of Respiratory and Critical Care Medicine 195 (#issue#): #pages#. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1274	Xu X., O'Quinn S., Hirsch I., Gopalan G. (2017//) Asthma symptom improvements with benralizumab are associated with improvements in activity functions and quality of life for patients with severe, uncontrolled asthma: results of pooled phase iii benralizumab studies. American Journal of Respiratory and Critical Care Medicine 195 (#issue#): #pages#. #notes#.	Pooled analysis of relevant RCTs
1275	Nelsen L.M., Gunsoy N., Cockle S.M., Albers F.C., Jones P.W. (2017//) Impact of asthma exacerbations on health related quality of life in patients with severe asthma. American Journal of Respiratory and Critical Care Medicine 195 (#issue#): #pages#. #notes#.	Pooled analysis of relevant RCTs
1277	Chanez P., McDonald M., Garin M., Murphy K. (2017//) Early decreases in blood eosinophil levels with reslizumab. American Journal of Respiratory and Critical Care Medicine 195 (#issue#): #pages#. #notes#.	Pooled analysis of relevant RCTs
1278	O'Quinn S., Xu X., Hirsch I., Gopalan G. (2017//) Improvement in patient-reported activity impairment, stress, and tiredness in patients with severe, uncontrolled asthma with eosinophilic inflammation: Pooled results from two phase III trials of benralizumab. American Journal of Respiratory and Critical Care Medicine 195 (#issue#): #pages#. #notes#.	Duplicate
1279	Trevor J.L., Albers F.C., Nelsen L.M., Bratton D.J., Wang-Jairaj J., Bradford E. (2017//) Effect of mepolizumab on health status, lung function and asthma control according to baseline blood eosinophil count in patients with severe eosinophilic asthma. American Journal of Respiratory and Critical Care Medicine 195 (#issue#): #pages#. #notes#.	Duplicate
1282	Wechsler M.E., Korn S., Sun S.X., Garin M. (2017//) Impact of reslizumab on healthcare resource utilization in adult patients with severe eosinophilic asthma. American Journal of Respiratory and Critical Care Medicine 195 (#issue#): #pages#. #notes#.	Duplicate

1285	Xu X., O'Quinn S., Hirsch I., Gopalan G. (2017//) Impact of asthma control status on lung function and patient well-being assessments in patients with severe asthma. American Journal of Respiratory and Critical Care Medicine 195 (#issue#): #pages#. #notes#.	Duplicate
1292	Eldegeir M.Y., Chapman A.A., Ferwana M., Caldron M. (2017//) Does the combination of omalizumab and Subcutaneous allergen immunotherapy (SCIT) have an add-on benefit to the efficacy and safety of allergen immunotherapy in asthma and allergic rhinitis? Systematic review. Clinical and Translational Allergy 7 (Supplement 2): #pages#. #notes#.	Incomplete/Insufficient/Partial data
1298	FitzGerald J.M., Ohta K., Adachi M., Tohda Y., Kamei T., Kato M., Takanuma M., Kakuno T., Imai N., Wu Y., Aurivillius M., Goldman M. (2017//) Benralizumab reduces exacerbations in Japanese patients with severe, uncontrolled asthma: subgroup analysis of the calima trial. Journal of Allergy and Clinical Immunology 139 (2 Supplement 1): AB10. #notes#.	Subgroup analysis not of interest
1299	Yancey S.W., Gunsoy N.B., Bradford E.S., Albers F.C., Prazma C.M., Follows R., Keene O.N., Pavord I. (2017//) Meta-analysis of mepolizumab global studies suggest consistent therapeutic response across a range of demographic sub-groups. Journal of Allergy and Clinical Immunology 139 (2 Supplement 1): AB9. #notes#.	On topic SLR/MA/NMA
1301	Liu M.C., Keene O.N., Yancey S.W., Bratton D.J., Albers F.C. (2017//) Efficacy of mepolizumab in patients with severe eosinophilic asthma and nasal polyps. Journal of Allergy and Clinical Immunology 139 (2 Supplement 1): AB8. #notes#.	On topic SLR/MA/NMA
1302	Katial R., Hoyte F., Germinaro M., McDonald M. (2017//) Efficacy of reslizumab in asthma patients with aspirin sensitivity and elevated blood eosinophils. Journal of Allergy and Clinical Immunology 139 (2 Supplement 1): AB8. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1307	Maselli DJ, Peters JI (2017//) 2017 - In severe asthma, benralizumab reduced daily oral glucocorticoid dose and asthma exacerbations at 6 months. #journal# 167 (8): 1. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1308	(2017//) Dupilumab improves lung function and reduces severe exacerbations in uncontrolled persistent asthma patients with high and low reversibility. Dupilumab improves lung function and reduces severe exacerbations in uncontrolled persistent asthma patients with high and low reversibility 50 (#issue#): #pages#. #notes#.	Duplicate
1309	(2017//) Dupilumab improves patient-reported outcomes in uncontrolled persistent asthma patients with ongoing allergic rhinitis. Dupilumab improves patient-reported outcomes in uncontrolled persistent asthma patients with ongoing allergic rhinitis 50 (#issue#): #pages#. #notes#.	Duplicate
1310	Lupinek C, Derfler K, Lee S, Prikoszovich T, Movadat O, Wollmann E, Cornelius C, Weber M, Froschl R, Selb R, Blatt K, Smiljkovic D, Schoder V, Cervenka R, Plaichner T, Stegfellner G, Huber H, Henning R, Kozik-Jaromin J, Perkmann T, Niederberger V, Petkov V, Valent P, Gauly A, Leinenbach HP, Uhlenbusch-Koerwer I, Valenta R (2017//) Extracorporeal IgE Immunoadsorption in Allergic Asthma: safety and Efficacy. #journal# 17 (#issue#): 119. #notes#.	Intervention/Comparator
1316	NCT03170271 (2017//) A Study of the Safety and Effectiveness of Benralizumab to Treat Patients With Severe Uncontrolled Asthma. A Multicenter, Randomized, Double-blind, Parallel Group, Placebo Controlled, Phase 3b Study to Evaluate the Safety and Efficacy of Benralizumab 30 mg sc in Patients With Severe Asthma Uncontrolled on Standard of Care Treatment #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
1318	NCT03052725 (2017//) A Study of Reslizumab in Patients 12 Years of Age and Older With Severe Eosinophilic Asthma. An Open-Label Extension Study of	Intervention/Comparator

	Reslizumab 110-mg Fixed, Subcutaneous Dosing in Patients 12 Years of Age and Older With Severe Eosinophilic Asthma #volume# (#issue#): #pages#. #notes#.	
1319	NCT03112577 (2017//) Study of REGN3500 and Dupilumab in Patients With Asthma. A Randomized, Placebo-controlled, Parallel Panel Study to Assess the Effects of REGN3500, Dupilumab, and Combination of REGN3500 Plus Dupilumab on Markers of Inflammation After Bronchial Allergen Challenge in Patients With Allergic Asthma #volume# (#issue#): #pages#. #notes#.	Population
1320	NCT03292588 (2017//) A Trial of Mepolizumab Adjunctive Therapy for the Prevention of Asthma Exacerbations in Urban Children. Mechanisms Underlying Asthma Exacerbations Prevented and Persistent With Immune-Based Therapy: a Systems Approach Phase 2 (ICAC-30) #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
1322	NCT03476109 (2017//) Study of Magnitude and Prediction of Response to Omalizumab and Mepolizumab in Adult Severe Asthma. Predictive Factors and Magnitude of Response to Omalizumab and Mepolizumab in Allergic and Eosinophilic Severe Asthma: a Pragmatic Multicenter Trial in Belgium #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
1323	Nelsen L, S Bradford E, Bratton DJ, Albers FC, Brusselle G (2017//) Improvement in rhinosinusitis health related quality of life in patients with severe eosinophilic asthma. #journal# 50 (#issue#): #pages#. #notes#.	Subgroup analysis not of interest
1325	(2017//) Exacerbation utilities and durations by type: estimates from Phase III benralizumab studies. Exacerbation utilities and durations by type: estimates from Phase III benralizumab studies 50 (#issue#): #pages#. #notes#.	Duplicate
1326	(2017//) Reslizumab for uncontrolled eosinophilic asthma in patients who experienced a single exacerbation in the previous year: sub-analysis of two phase 3 trials. Reslizumab for uncontrolled eosinophilic asthma in patients who experienced a single exacerbation in the previous year: sub-analysis of two phase 3 trials 50 (#issue#): #pages#. #notes#.	Subgroup analysis not of interest
1327	(2017//) Efficacy of reslizumab in adults with severe eosinophilic asthma with >=3 exacerbations in the previous year: analyses at weeks 16 and 52 of two placebo-controlled phase 3 trials. Efficacy of reslizumab in adults with severe eosinophilic asthma with >=3 exacerbations in the previous year: analyses at weeks 16 and 52 of two placebo-controlled phase 3 trials 50 (#issue#): #pages#. #notes#.	Duplicate
1328	(2017//) A longitudinal follow-up of severe asthma patients receiving reslizumab. A longitudinal follow-up of severe asthma patients receiving reslizumab 50 (#issue#): #pages#. #notes#.	Duplicate
1329	(2017//) Benralizumab attenuates airway eosinophilopoietic processes in prednisone-dependent asthma. Benralizumab attenuates airway eosinophilopoietic processes in prednisone-dependent asthma 50 (#issue#): #pages#. #notes#.	Duplicate
1330	(2017//) Characterisation of exacerbations of severe eosinophilic asthma (SEA) on mepolizumab compared to placebo. Characterisation of exacerbations of severe eosinophilic asthma (SEA) on mepolizumab compared to placebo 50 (#issue#): #pages#. #notes#.	Duplicate
1331	(2017//) Mepolizumab in patients >=3 exacerbations and eosinophil count >=300 cells/[mu]L. Mepolizumab in patients >=3 exacerbations and eosinophil count >=300 cells/[mu]L 50 (#issue#): #pages#. #notes#.	Pooled analysis of relevant RCTs
1332	(2017//) Characterizing responders to benralizumab for severe asthma: pooled analysis of the SIROCCO and CALIMA studies. Characterizing responders to	Duplicate

	benralizumab for severe asthma: pooled analysis of the SIROCCO and CALIMA studies 50 (#issue#): #pages#. #notes#.	
1333	Maspero JF, Katelaris C, Jayawardena S, Rowe P, Maroni J, Pirozzi G, Amin N, Graham NMH, Mannent L, Teper A (2017//) Dupilumab efficacy in uncontrolled persistent asthma patients with history of comorbid chronic rhinosinusitis with or without nasal polyps. #journal# 195 (no pagination): #pages#. #notes#.	Duplicate
1334	(2017//) Dupilumab efficacy and effect on asthma control in patients with uncontrolled persistent asthma and comorbid chronic rhinosinusitis with or without nasal polyps. Dupilumab efficacy and effect on asthma control in patients with uncontrolled persistent asthma and comorbid chronic rhinosinusitis with or without nasal polyps 47 (Suppl 5): 22. #notes#.	Duplicate
1335	Brusselle G, Canvin J, Weiss S, Sun SX, Buhl R (2017//) Stratification of eosinophilic asthma patients treated with reslizumab and GINA step 4 or 5 therapy. #journal# 3 (3): #pages#. #notes#.	Duplicate
1337	Nair P, Wenzel SE, Rabe K-F, Bourdin A, Lugogo N, Kuna P, Barker P, Sproule S, Ponnarambil S, Goldman M (2017//) Benralizumab significantly reduced oral corticosteroid dosages and asthma exacerbation rates for patients with severe, uncontrolled asthma: results of the zonda phase III trial. #journal# 195 (#issue#): #pages#. #notes#.	Duplicate
1338	Busse WW, Chipps BE, Rosen K, Ortiz B, Haselkorn T, Trzaskoma BL, Lanier BQ, Szefler SJ (2017//) Asthma exacerbations and lung function decline in a pooled analysis of adolescents and adults from randomized controlled trials of omalizumab. #journal# 195 (#issue#): #pages#. #notes#.	Duplicate
1339	Chupp G, Albers FC, Nelsen LM, Bratton DJ, Wang-Jairaj J, Bradford E, Jones PW (2017//) Treatment response of mepolizumab on health status and asthma control in patients with severe eosinophilic asthma. #journal# 195 (#issue#): #pages#. #notes#.	Duplicate
1340	Chanez P, McDonald M, Garin M, Murphy K (2017//) Early decreases in blood eosinophil levels with reslizumab. #journal# 195 (#issue#): #pages#. #notes#.	Duplicate
1344	Wechsler ME, Korn S, Sun SX, Garin M (2017//) Impact of reslizumab on healthcare resource utilization in adult patients with severe eosinophilic asthma. #journal# 195 (#issue#): #pages#. #notes#.	Pooled analysis of relevant RCTs
1345	Prazma C, Bel E, Price R, Bradford E, Albers FC, Yancey S (2017//) Oral corticosteroid dose modulation in severe asthma: impact on peripheral blood eosinophil count. #journal# 195 (#issue#): #pages#. #notes#.	Duplicate
1347	Chanez P, Garin M, McDonald M, Humbert M (2017//) Reslizumab reduces severe exacerbations associated with emergency department visit or hospitalization and improves measures of lung function in patients on maintenance oral corticosteroids (OCS) at baseline. #journal# 50 (#issue#): #pages#. #notes#.	Duplicate
1348	Wang B, Chia YL, Yu B, Barker P, Goldman M, Roskos L (2017//) Relationship between benralizumab exposure and asthma exacerbation rate for patients with severe asthma. #journal# 50 (#issue#): #pages#. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1351	Albers F, Nelsen LM, Bratton DJ, Bradford ES, Braunstahl GJ (2017//) Mepolizumab improves activity limitation in severe eosinophilic asthma. #journal# 50 (#issue#): #pages#. #notes#.	Duplicate
1352	Virchow JC, Garin M, McDonald M, Buhl R (2017//) Clinically meaningful FEV1 response with reslizumab achieved early and sustained over 52 weeks. #journal# 50 (#issue#): #pages#. #notes#.	Duplicate

1353	Wang B, Yan L, Yu B, Barker P, Goldman M, Roskos L (2017//) Longitudinal modeling of prebronchodilator FEV1 response to benralizumab for patients with severe asthma. #journal# 50 (#issue#): #pages#. #notes#.	Duplicate
1354	Shrimanker R, Hargaden B, Bradding P, Wardlaw A, Brightling CE, Green R, Bafadhel M, Heaney L, Pavord I, Haldar P (2017//) Mepolizumab and the response to oral prednisolone in patients with severe eosinophilic asthma. #journal# 50 (#issue#): #pages#. #notes#.	Duplicate
1355	Bjermer L, Garin M, Sun SX (2017//) Clinically meaningful improvements with reslizumab in patient-reported outcomes and lung function in a sub-population defined by the EU indication with >=3 exacerbations. #journal# 50 (#issue#): #pages#. #notes#.	Duplicate
1356	Fang L, Roth M, Sun Q, Savic S, Tamm M, Stolz D (2017//) Late Breaking Abstract-Bronchial Thermoplasty restores constitutive high PRMT1 expression in asthmatic airways. #journal# 50 (#issue#): #pages#. #notes#.	Intervention/Comparator
1358	(2017//) Asthma symptom improvements with benralizumab are associated with improvements in activity functions and quality of life for patients with severe, uncontrolled asthma. Asthma symptom improvements with benralizumab are associated with improvements in activity functions and quality of life for patients with severe, uncontrolled asthma Conference: 22nd Congress of the Asian Pacific Society of Respirology, ASPR 2017. Australia. 22 (Supplement 3): 168. #notes#.	Duplicate
1360	(2017//) Asthma symptom improvements with benralizumab are associated with improvements in activity functions and quality of life for patients with severe, uncontrolled asthma: results of pooled phase iii benralizumab studies. Asthma symptom improvements with benralizumab are associated with improvements in activity functions and quality of life for patients with severe, uncontrolled asthma: results of pooled phase iii benralizumab studies Conference: British Thoracic Society Winter Meeting, BTS 2017. United Kingdom. 72 (Supplement 3): A118. #notes#.	Pooled analysis of relevant RCTs
1361	(2017//) Differences in distributional properties and responsiveness between a generic (EQ-5D) and disease-specific (ASUI) utility instrument in patients with severe eosinophilic asthma. Differences in distributional properties and responsiveness between a generic (EQ-5D) and disease-specific (ASUI) utility instrument in patients with severe eosinophilic asthma Conference: ISPOR 20th Annual European Congress. United Kingdom. 20 (9): A648. #notes#.	Duplicate
1362	(2017//) Efficacy of benralizumab for patients with severe, uncontrolled atopic asthma by serum immunoglobulin e concentrations. Efficacy of benralizumab for patients with severe, uncontrolled atopic asthma by serum immunoglobulin e concentrations Conference: 2017 Annual Scientific Meeting of the American College of Allergy, Asthma and Immunology. United States. 119 (5 Supplement 1): S56. #notes#.	Duplicate
1363	Gunsoy NB, Cockle SM, Yancey SW, Keene ON, Bradford ES, Albers FC, Pavord ID (2017//) Evaluation of Potential Continuation Rules for Mepolizumab Treatment of Severe Eosinophilic Asthma. #journal# (no pagination) (#issue#): #pages#. #notes#.	Duplicate
1364	(2017//) Asthma control in patients with severe eosinophilic asthma treated with mepolizumab. Asthma control in patients with severe eosinophilic asthma treated with mepolizumab Conference: American Thoracic Society International Conference, ATS 2017. United States. 195 (no pagination): #pages#. #notes#.	Duplicate
1365	Chupp GL, Bradford ES, Albers FC, Bratton DJ, Wang-Jairaj J, Nelsen LM, Trevor JL, Magnan A, ten Brinke A (2017//) Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe	Duplicate

	eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. #journal# (no pagination) (#issue#): #pages#. #notes#.	
1366	Goldman M, Hirsch I, Zangrilli JG, Newbold P, Xu X (2017//) The association between blood eosinophil count and benralizumab efficacy for patients with severe, uncontrolled asthma: subanalyses of thePhase III SIROCCO and CALIMA studies. #journal# #volume# (#issue#): 1. #notes#.	Duplicate
1367	(2017//) Association between blood eosinophil count and benralizumab efficacy for adult patients with severe, uncontrolled asthma. Association between blood eosinophil count and benralizumab efficacy for adult patients with severe, uncontrolled asthma Conference: 2017 Annual Scientific Meeting of the American College of Allergy, Asthma and Immunology. United States. 119 (5 Supplement 1): S55. #notes#.	Duplicate
1368	(2017//) Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies #volume# (#issue#): #pages#. #notes#.	Duplicate
1369	(2017//) Effects of immunoglobulin e concentration, eosinophil concentration, and atopy status on benralizumab efficacy in asthma. Effects of immunoglobulin e concentration, eosinophil concentration, and atopy status on benralizumab efficacy in asthma Conference: 2017 Annual Scientific Meeting of the American College of Allergy, Asthma and Immunology. United States. 119 (5 Supplement 1): S56. #notes#.	Duplicate
1374	Casale TB, Chipps BE, Rosen K, Trzaskoma B, Haselkorn T, Omachi TA, Greenberg S, Hanania NA (2017//) Response to omalizumab using patient enrichment criteria from trials of novel biologics in asthma. #journal# (no pagination) (#issue#): #pages#. #notes#.	Duplicate
1376	Brusselle G, Canvin J, Weiss S, Sun SX, Buhl R (2017//) Stratification of eosinophilic asthma patients treated with reslizumab and GINA step 4 or 5 therapy. #journal# 3 (3) (no pagination): #pages#. #notes#.	Duplicate
1377	Papi A, Swanson BN, Staudinger H, Rowe P, Maroni J, Jayawardena S, Hamilton J, Amin N, Pirozzi G, Akinlade B, Graham NMH, Teper A (2017//) Dupilumab rapidly and significantly improves lung function and decreases inflammation by 2 weeks after treatment initiation in patients with uncontrolled persistent asthma. #journal# 195 (no pagination): #pages#. #notes#.	Duplicate
1378	Humbert M, Castro M, McDonald M, Germinaro M (2017//) Efficacy of reslizumab in asthma patients eligible for omalizumab treatment. #journal# 195 (no pagination): #pages#. #notes#.	Duplicate
1380	Xu X, O'Quinn S, Hirsch I, Gopalan G (2017//) Asthma symptom improvements with benralizumab are associated with improvements in activity functions and quality of life for patients with severe, uncontrolled asthma: results of pooled phase iii benralizumab studies. #journal# 195 (no pagination): #pages#. #notes#.	Duplicate
1381	Nelsen LM, Gunsoy N, Cockle SM, Albers FC, Jones PW (2017//) Impact of asthma exacerbations on health related quality of life in patients with severe asthma. #journal# 195 (no pagination): #pages#. #notes#.	Duplicate
1382	O'Quinn S, Xu X, Hirsch I, Gopalan G (2017//) Improvement in patient-reported activity impairment, stress, and tiredness in patients with severe, uncontrolled asthma with eosinophilic inflammation: pooled results from two phase III trials of benralizumab. #journal# 195 (no pagination): #pages#. #notes#.	Pooled analysis of relevant RCTs

1384	Xu X, O'Quinn S, Hirsch I, Gopalan G (2017//) Impact of asthma control status on lung function and patient well-being assessments in patients with severe asthma. #journal# 195 (no pagination): #pages#. #notes#.	Pooled analysis of relevant RCTs
1418	Matin, N, Tabatabaie, O, Falsaperla, R, Pavone, P, Serra, A, Cocuzza, S, Di Mauro, P, Licciardello, L, Lubrano, R, Vitaliti, G (2016//) Efficacy and safety of omalizumab in paediatric age: an update of literature data.. Journal of biological regulators and homeostatic agents 30 (2): 579. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1423	Einecke, Dirk (2016//) [New therapies turn oral steroids into reserve agents].. MMW Fortschritte der Medizin 158 (11): 79. #notes#.	Non-English
1426	Einecke, Dirk (2016//) [Oral steroids downgraded, biologics upgraded].. MMW Fortschritte der Medizin 158 (10): 86. #notes#.	Non-English
1433	Jager-Becker, Dagmar (2016//) [Severe refractory eosinophilic asthma].. MMW Fortschritte der Medizin 158 (3): 67. #notes#.	Non-English
1436	Einecke, Dirk (2016//) [First therapy option for severe eosinophilic asthma].. MMW Fortschritte der Medizin 158 (7): 70. #notes#.	Non-English
1437	Stiefelhagen, Peter (2016//) [Therapy goal is asthma control].. MMW Fortschritte der Medizin 158 (7): 20. #notes#.	Non-English
1445	Morrow, Thomas (2016//) Enter Mepolizumab, Better Late Than Never.. Managed care (Langhorne, Pa.) 25 (1): 42. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1448	Anonymous (2016//) Mepolizumab (Nucala) for severe eosinophilic asthma.. The Medical letter on drugs and therapeutics 58 (1486): 11. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1465	Pham T.-H., Damera G., Newbold P., Ranade K. (2016//) Reductions in eosinophil biomarkers by benralizumab in patients with asthma. Respiratory Medicine 111 (#issue#): 21. #notes#.	Population
1468	Wang F.-P., Liu T., Lan Z., Li S.-Y., Mao H. (2016//) Efficacy and safety of anti-Interleukin-5 Therapy in patients with asthma: A systematic review and meta-Analysis. PLoS ONE 11 (11): e0166833. #notes#.	On topic SLR/MA/NMA
1471	Pillai P., Chan Y.-C., Wu S.-Y., Line O.-L., Thomas C., Durham S.R., Andrew M.-G., Rajakulasingam R.K., Ying S., Gould H.J., Corrigan C.J. (2016//) Omalizumab reduces bronchial mucosal IgE and improves lung function in non-Atopic asthma. European Respiratory Journal 48 (6): 1593. #notes#.	Incomplete/Insufficient/Partial data
1477	Lugogo N., Domingo C., Chanez P., Leigh R., Gilson M.J., Price R.G., Yancey S.W., Ortega H.G. (2016//) Long-term Efficacy and Safety of Mepolizumab in Patients With Severe Eosinophilic Asthma: A Multi-center, Open-label, Phase IIIb Study. Clinical Therapeutics 38 (9): 2058. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1491	Park H.-S., Kim M.-K., Imai N., Nakanishi T., Adachi M., Ohta K., Tohda Y. (2016//) A phase 2a study of benralizumab for patients with eosinophilic asthma in South Korea and Japan. International Archives of Allergy and Immunology 169 (3): 135. #notes#.	Intervention/Comparator
1500	Nguyen V.Q., Ulrik C.S. (2016//) Measures to reduce maintenance therapy with oral corticosteroid in adults with severe asthma. Allergy and Asthma Proceedings 37 (6): e125. #notes#.	On topic SLR/MA/NMA
1507	Wenzel S., Castro M., Corren J., Maspero J., Wang L., Zhang B., Pirozzi G., Sutherland E.R., Evans R.R., Joish V.N., Eckert L., Graham N.M.H., Stahl N., Yancopoulos G.D., Louis-Tisserand M., Teper A. (2016//) Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting beta2 agonist: a	Duplicate

	randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. The Lancet 388 (10039): 31. #notes#.	
1514	Brusselle G., McElhattan J., Canvin J., Buhl R. (2016//) Reslizumab (RES) in asthma patients (pts) with severe eosinophilic asthma stratified by GINA asthma steps 4 and 5: Analysis of two phase 3, placebo (PBO)-controlled trials. European Respiratory Journal 48 (Supplement 60): #pages#. #notes#.	Pooled analysis of relevant RCTs
1515	Pouliquen I., Austin D., Gunsoy N., Yancey S. (2016//) A weight-based exacerbation dose-response analysis of mepolizumab in severe asthma with eosinophilic phenotype. European Respiratory Journal 48 (Supplement 60): #pages#. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1517	Austin D., Pouliquen I., Keene O., Yancey S. (2016//) Blood eosinophil dose response to oral corticosteroids in a population of patients with severe asthma. European Respiratory Journal 48 (Supplement 60): #pages#. #notes#.	Pooled analysis of relevant RCTs
1525	Wenzel S., Swanson B., Teper A., Hamilton J., Izuhara K., Ohta S., Ono J., Zhu H., Zhang B., Staudinger H., Graham N.M.H., Pirozzi G. (2016//) Dupilumab reduces severe exacerbations in periostin-high and periostin-low asthma patients. European Respiratory Journal 48 (Supplement 60): #pages#. #notes#.	Subgroup analysis not of interest
1526	Virchow J.C., Zangrilli J., Weiss S., Korn S. (2016//) Reslizumab (RES) in patients (pts) with inadequately controlled asthma and elevated blood eosinophils (EOS): Analysis of two phase 3, placebo-controlled trials. European Respiratory Journal 48 (Supplement 60): #pages#. #notes#.	Pooled analysis of relevant RCTs
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1723	Lowe P.J., Bottoli I., Arm J., Skerjanec A., Groenewegen A., Maahs S. (2015//) A PKPD mathematical model to determine efficacy of multiple doses of QGE031 (ligelizumab) vs. omalizumab and placebo in inhibiting skin responses in atopic asthmatics. European Respiratory Journal 46 (SUPPL. 59): #pages#. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1725	Yang J., Humphries M., Ren S., Wang L., Pethe A., Kottakis I. (2015//) Evaluation of omalizumab therapy in a Chinese versus predominantly Caucasian population: Comparison of clinical data. European Respiratory Journal 46 (SUPPL. 59): #pages#. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
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1802	Brusselle G, Germinaro M, Eid S, Zangrilli J (2015//) Reslizumab in patients with late-onset asthma with elevated blood eosinophils.. Reslizumab in patients with late-onset asthma with elevated blood eosinophils. 46 (no pagination): #pages#. #notes#.	Duplicate
1803	Lowe PJ, Bottoli I, Arm J, Skerjanec A, Groenewegen A, Maahs S (2015//) A PKPD mathematical model to determine efficacy of multiple doses of QGE031 (ligelizumab) vs. omalizumab and placebo in inhibiting skin responses in atopic asthmatics. #journal# 46 (#issue#): #pages#. #notes#.	Duplicate
1805	Wenzel S, Castro M, Zhang B, Pirozzi G, Sutherland ER, Graham N, et al (2015//) A dose-ranging study of dupilumab in patients (pts) with uncontrolled asthma despite use of inhaled corticosteroids plus a long-acting beta-agonist (ICS/LABA): Final data. #journal# #volume# (#issue#): #pages#. #notes#.	Duplicate
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1818	Anonymous (2014//) [Approaches to improving therapeutic success].. MMW Fortschritte der Medizin 156 (12): 62. #notes#.	Unavailable
1831	Fuesl, H S, Stiefelhagen, P (2014//) [Nearly uncontrollable hyperreactivity. Last options in bronchial asthma].. MMW Fortschritte der Medizin 156 (5): 17. #notes#.	Unavailable
1841	Thomson, Neil C (2014//) Omalizumab decreases exacerbations and allows a step down in daily inhaled corticosteroid dose in adults and children with moderate-to-severe asthma.. Evidence-based medicine 19 (4): 135. Comment on (CON).	Study design (non-RCT, opinion, commentary, single-arm, etc)
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1870	Castro M., Wenzel S.E., Bleecker E.R., Pizzichini E., Kuna P., Busse W.W., Gossage D.L., Ward C.K., Wu Y., Wang B., Khatry D.B., van der Merwe R., Kolbeck R., Molfino N.A., Raible D.G. (2014//) Benralizumab, an anti-interleukin 5 receptor alpha monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: A phase 2b randomised dose-ranging study. The Lancet Respiratory Medicine 2 (11): 878. #notes#.	Intervention/Comparator
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1904	Busse W.W., Trzaskoma B., Omachi T.A., Canvin J., Rosen K., Chipps B.E., Luskin A.T., Solari P.G. (2014//) Evaluating xolair persistency of response after long-term therapy (XPORT). American Journal of Respiratory and Critical Care Medicine 189 (MeetingAbstracts): #pages#. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
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1910	Castro M., Gossage D.L., Ward C.K., Wu Y., Khatri D.B., Molfino N.A., Raible D.G. (2014//) Benralizumab reduces exacerbations and improves lung function in adults with uncontrolled eosinophilic asthma. American Journal of Respiratory and Critical Care Medicine 189 (MeetingAbstracts): #pages#. #notes#.	Intervention/Comparator
1912	Busse W., Trazskoma B., Omachi T., Canvin J., Rosen K., Chipps B., Luskin A., Solari P. (2014//) Evaluating omalizumab persistency of response after long-term therapy (XPORT). European Respiratory Journal 44 (SUPPL. 58): #pages#. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1913	Bousquet J., Rao S., Manga V. (2014//) Global evaluation of treatment effectiveness (GETE) is an accurate predictor of response to omalizumab in patients with severe allergic asthma: A pooled analysis. European Respiratory Journal 44 (SUPPL. 58): #pages#. #notes#.	Pooled analysis of relevant RCTs
1914	Kasujee I., Bader G. (2014//) Omalizumab add-on therapy reduces exacerbations among responders: A pooled NNT analysis from 5 phase 3 studies. European Respiratory Journal 44 (SUPPL. 58): #pages#. #notes#.	Pooled analysis of relevant RCTs
1916	Castro M., Wenzel S., Kolbeck R., Khatry D., Christine W., Wu Y., Van Der Merwe R., Bleecker E. (2014//) Late-breaking abstract: A phase 2 study of benralizumab on exacerbations, lung function, and asthma control in adults with uncontrolled eosinophilic asthma. European Respiratory Journal 44 (SUPPL. 58): #pages#. #notes#.	Duplicate
1921	Eck S., Castro M., Sinibaldi D., White W., Folliot K., Gossage D., Wu Y., Raible D., Roskos L., Kolbeck R., Ward C. (2014//) Benralizumab effect on blood basophil counts in adults with uncontrolled asthma. European Respiratory Journal 44 (SUPPL. 58): #pages#. #notes#.	Intervention/Comparator
1924	Bel E.H., Wenzel S.E., Thompson P.J., Prazma C.M., Keene O., Yancey S.W., Ortega H., Pavord I.D. (2014//) Late-breaking abstract: Oral corticosteroid-sparing effect of mepolizumab in severe eosinophilic asthma: The SIRIUS study. European Respiratory Journal 44 (SUPPL. 58): #pages#. #notes#.	Duplicate
1925	Ortega H., Liu M., Pavord I., Brusselle G., FitzGerald J.M., Chetta A., Katz L., Keene O., Yancey S., Chanez P. (2014//) Late-breaking abstract: Reduction in exacerbations with mepolizumab in severe eosinophilic asthma: MENSA study. European Respiratory Journal 44 (SUPPL. 58): #pages#. #notes#.	Duplicate
1930	Antonova J., Trzaskoma B., Raimundo K., Solari P., Zazzali J. (2014//) Longitudinal change in asthma symptom control in patients who continued vs. discontinued omalizumab: Results from the xport study. Annals of Allergy, Asthma and Immunology 113 (5 SUPPL. 1): A37. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)

1941	Bergrath E., Hwa Ong S., Bousquet J., Balwin M., Manga V., Rao S., Cope S. (2014//) Systematic review of observational studies and RCTS of omalizumab in severe persistent allergic asthma and meta-analysis feasibility assessment. Value in Health 17 (7): A589. #notes#.	Incomplete/Insufficient/Partial data
1950	Swanson B., Ming J., Ren H., Wang L., Wenzel S., Beck L., Diciccio T., Li Y., Belomestnov P., Graham N., Pirozzi G., Hamilton J. (2014//) Dupilumab suppresses Th2 inflammation in adult asthma and atopic dermatitis. World Allergy Organization Journal 7 (SUPPL. 1): #pages#. #notes#.	Intervention/Comparator
1951	Swanson B.N., Wang L., Ming J., Hamilton J.D., Teper A., Dicioccio T., Li Y., Graham N., Pirozzi G., Wenzel S.E. (2014//) Exhaled nitric oxide (FENO) and t-helper 2 cell biomarkers: Can they predict treatment response to dupilumab, an il-4ra antibody, in an eosinophilic asthma population?. Journal of Allergy and Clinical Immunology 133 (2 SUPPL. 1): AB85. #notes#.	Intervention/Comparator
1954	Paterniti MO, Breslin LM, Courneya JP, Sterba PM, Hamilton RG, MacGlashan DW, Saini SS (2014//) Differences in effects of omalizumab on late-phase responses to allergen challenge in the skin and nose at the time of basophil hyporesponsiveness. #journal# 134 (6): 1743. #notes#.	Population
1962	NCT02054130 (2014//) Study to Evaluate the Efficacy and Safety of MEDI9929 (AMG 157) in Adult Subjects With Inadequately Controlled, Severe Asthma. A Phase 2 Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of MEDI9929 in Adult Subjects With Inadequately Controlled, Severe Asthma #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
1973	Haldar P, Brightling C E, Singapuri A, Hargadon B, Gupta S, Monteiro W, et al (2014//) Outcomes after cessation of mepolizumab therapy in severe eosinophilic asthma: a 12-month follow-up analysis. #journal# 133 (3): 921. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
1975	Corren J, Weinstein S, Janka L, O'Brien C, Zangrilli J (2014//) A randomized phase 3 study of reslizumab efficacy in relation to blood eosinophil levels in patients with moderate to severe asthma. #journal# 44 (Suppl 58): 4673. #notes#.	Duplicate
1976	Eck S, Castro M, Sinibaldi D, White W, Folliot K, Gossage D, et al (2014//) Benralizumab effect on blood basophil counts in adults with uncontrolled asthma. #journal# 44 (Suppl 58): P297. #notes#.	Duplicate
1977	Bjermer L, Lemiere C, Maspero J, Ciesielska M, O'Brien C, Zangrilli J (2014//) A randomized phase 3 study of the efficacy and safety of reslizumab in subjects with asthma with elevated eosinophils. #journal# 44 (#issue#): #pages#. #notes#.	Duplicate
1978	Eck S, Castro M, Sinibaldi D, White W, Folliot K, Gossage D, Wu Y, Raible D, Roskos L, Kolbeck R, Ward C (2014//) Benralizumab effect on blood basophil counts in adults with uncontrolled asthma. #journal# 44 (#issue#): #pages#. #notes#.	Duplicate
1979	Corren J, Weinstein S, Janka L, O'Brien C, Zangrilli J (2014//) A randomized phase 3 study of reslizumab efficacy in relation to blood eosinophil levels in patients with moderate to severe asthma. #journal# 44 (#issue#): #pages#. #notes#.	Duplicate
1980	Wang B, Yan L, Hutmacher M, White WI, Ward CK, Nielsen J, Wu Y, Goldman M, Raible DG, Roskos L (2014//) Exposure-response analysis for determination of benralizumab optimal dosing regimen in adults with asthma. #journal# 189 (no pagination): #pages#. #notes#.	Duplicate

1981	Ortega H, Chupp G, Bardin P, Bourdin A, Garcia G, Hartley B, Yancey S, Humbert M (2014//) The role of mepolizumab in atopic and nonatopic severe asthma with persistent eosinophilia. #journal# 44 (1): 239. #notes#.	Intervention/Comparator
1982	Wenzel SE, Teper A, Wang L, Pirozzi G, Radin A, Graham N, Castro M (2014//) ACQ5 improvement with dupilumab in patients with persistent asthma and elevated eosinophil levels: Responder analysis from a 12-week proof-of-concept placebo-controlled trial.. #journal# 189 (no pagination): #pages#. #notes#.	Duplicate
1983	Castro M, Teper A, Wang L, Pirozzi G, Radin A, Graham N, Weinstein S, Wenzel SE (2014//) Responder analysis for fev1 improvement with dupilumab in patients with persistent asthma and elevated eosinophil levels.. #journal# 189 (no pagination): #pages#. #notes#.	Duplicate
1984	Castro M, Gossage DL, Ward CK, Wu Y, Khatri DB, Molfino NA, Raible DG (2014//) Benralizumab reduces exacerbations and improves lung function in adults with uncontrolled eosinophilic asthma.. #journal# 189 (no pagination): #pages#. #notes#.	Duplicate
1986	Busse WW, Trzaskoma B, Omachi TA, Canvin J, Rosen K, Chipps BE, Luskin AT, Solari PG (2014//) Evaluating xolair persistency of response after long-term therapy (XPORT).. #journal# 189 (no pagination): #pages#. #notes#.	Duplicate
1988	Busse W, Trazskoma B, Omachi T, Canvin J, Rosen K, Chipps B, Luskin A, Solari P (2014//) Evaluating omalizumab persistency of response after long-term therapy (XPORT).. #journal# 44 (#issue#): #pages#. #notes#.	Duplicate
1989	Kasujee I, Bader G (2014//) Omalizumab add-on therapy reduces exacerbations among responders: A pooled NNT analysis from 5 phase 3 studies.. #journal# 44 (#issue#): #pages#. #notes#.	Duplicate
1990	Castro M, Wenzel S, Kolbeck R, Khatry D, Christine W, Wu Y, Van Der Merwe R, Bleecker E (2014//) Late-breaking abstract: A phase 2 study of benralizumab on exacerbations, lung function, and asthma control in adults with uncontrolled eosinophilic asthma.. #journal# 44 (#issue#): #pages#. #notes#.	Intervention/Comparator
1991	Bousquet J, Rao S, Manga V (2014//) Global evaluation of treatment effectiveness (GETE) is an accurate predictor of response to omalizumab in patients with severe allergic asthma: A pooled analysis.. #journal# 44 (#issue#): #pages#. #notes#.	Duplicate
1997	Castro M, Wenzel S, Kolbeck R, Khatry D, Christine W, Wu Y, et al (2014//) A phase 2 study of benralizumab on exacerbations, lung function, and asthma control in adults with uncontrolled eosinophilic asthma [Abstract]. #journal# 44 (Suppl 58): 2909. #notes#.	Intervention/Comparator
1998	Gauvreau G, Boulet L-P, Leigh R, Cockcroft DW, Davis BE, Mayers I, et al (2014//) Efficacy and safety of multiple doses of QGE031 (ligelizumab) versus omalizumab and placebo in inhibiting the allergen-induced early asthmatic response [Abstract]. #journal# 44 (Suppl 58): 2910. #notes#.	Population
2000	Robinson, Douglas S (2013//) Mepolizumab for severe eosinophilic asthma.. Expert review of respiratory medicine 7 (1): 13. Comment on (CON).	Intervention/Comparator
2015	Takaku, Yotaro, Soma, Tomoyuki, Nishihara, Fuyumi, Nakagome, Kazuyuki, Kobayashi, Takehito, Hagiwara, Koichi, Kanazawa, Minoru, Nagata, Makoto (2013//) Omalizumab attenuates airway inflammation and interleukin-5 production by mononuclear cells in patients with severe allergic asthma.. International archives of allergy and immunology 161 Suppl 2 (#issue#): 107. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)

2034	Dasgupta A., Zhang S., Thabane L., Nair P. (2013//) Sample sizes for clinical trials using sputum eosinophils as a primary outcome. European Respiratory Journal 42 (4): 1003. #notes#.	On topic SLR/MA/NMA
2045	Norman G., Faria R., Paton F., Llewellyn A., Fox D., Palmer S., Clifton I., Paton J., Woolacott N., McKenna C. (2013//) Omalizumab for the treatment of severe persistent allergic asthma: A systematic review and economic evaluation. Health Technology Assessment 17 (52): #pages#. #notes#.	On topic SLR/MA/NMA
2047	Liu Y., Zhang S., Li D.-W., Jiang S.-J. (2013//) Efficacy of Anti-Interleukin-5 Therapy with Mepolizumab in Patients with Asthma: A Meta-Analysis of Randomized Placebo-Controlled Trials. PLoS ONE 8 (3): e59872. #notes#.	On topic SLR/MA/NMA
2048	Kopp M.V., Hamelmann E., Bendiks M., Zielen S., Kamin W., Bergmann K.-C., Klein C., Wahn U. (2013//) Transient impact of omalizumab in pollen allergic patients undergoing specific immunotherapy. Pediatric Allergy and Immunology 24 (5): 427. #notes#.	Intervention/Comparator
2060	Laviolette M., Gossage D.L., Gauvreau G., Leigh R., Olivenstein R., Katial R., Busse W.W., Wenzel S., Wu Y., Datta V., Kolbeck R., Molfino N.A. (2013//) Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. Journal of Allergy and Clinical Immunology 132 (5): 1086. #notes#.	Intervention/Comparator
2061	Ayars A.G., Altman L.C., Potter-Perigo S., Radford K., Wight T.N., Nair P. (2013//) Sputum hyaluronan and versican in severe eosinophilic asthma. International Archives of Allergy and Immunology 161 (1): 65. #notes#.	Intervention/Comparator
2062	Wenzel S., Ford L., Pearlman D., Spector S., Sher L., Skobieranda F., Wang L., Kirkesseli S., Rocklin R., Bock B., Hamilton J., Ming J.E., Radin A., Stahl N., Yancopoulos G.D., Graham N., Pirozzi G. (2013//) Dupilumab in persistent asthma with elevated eosinophil levels. New England Journal of Medicine 368 (26): 2455. #notes#.	Intervention/Comparator
2065	Sorkness C.A., Wildfire J.J., Calatroni A., Mitchell H.E., Busse W.W., O'Connor G.T., Pongracic J.A., Ross K., Gill M.A., Kattan M., Morgan W.J., Teach S.J., Gergen P.J., Liu A.H., Szefler S.J. (2013//) Reassessment of omalizumab-dosing strategies and pharmacodynamics in inner-city children and adolescents. Journal of Allergy and Clinical Immunology: In Practice 1 (2): 163. #notes#.	Incomplete/Insufficient/Partial data
2067	Wenzel S.E., Pirozzi G., Wang L., Kirkesseli S., Rocklin R., Radin A., Skobieranda F. (2013//) Efficacy and safety of SAR231893/REGN668 in patients with moderate-to-severe, persistent asthma and elevated eosinophil levels. American Journal of Respiratory and Critical Care Medicine 187 (MeetingAbstracts): #pages#. #notes#.	Incomplete/Insufficient/Partial data
2069	Ortega H.G., Chupp G., Bardin P., Bourdin A., Hartley B., Humbert M. (2013//) The role of mepolizumab in atopic and non-atopic patients with refractory eosinophilic asthma. American Journal of Respiratory and Critical Care Medicine 187 (MeetingAbstracts): #pages#. #notes#.	Intervention/Comparator
2078	Djukanovic R., Wilson S.J., Castro M., Leigh R., Sutherland E.R., Canvin J., Peachey G., Ackrill J., Georgiou P., Chen C.-W. (2013//) Omalizumab in allergic eosinophilic asthma and lung eosinophil numbers: A 78-week randomized controlled trial. European Respiratory Journal 42 (SUPPL. 57): #pages#. #notes#.	Incomplete/Insufficient/Partial data
2079	Wenzel S., Ming J., Hamilton J., Radin A., Rocklin R., Hultsch T., Wang L., Skobieranda F., Pirozzi G. (2013//) Therapeutic blockade of IL-4 and 13 signaling with dupilumab (SAR231893/REGN668) inhibits key biomarkers in asthma. European Respiratory Journal 42 (SUPPL. 57): #pages#. #notes#.	Incomplete/Insufficient/Partial data

2086	Korn S., Schiffer T., Buhl R. (2013//) Anti-interleukin-5 in severe asthma: Blood eosinophilia predicts lung function improvement. European Respiratory Journal 42 (SUPPL. 57): #pages#. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
2107	Zakaria M., Abu-Hussein S., Abu-Hussein A., Ahmed M. (2013//) The effect of omalizumab in treatment of inadequate controlled severe persistent asthma patient. Chest 144 (4 MEETING ABSTRACT): #pages#. #notes#.	Incomplete/Insufficient/Partial data
2117	NCT01914757 (2013//) Efficacy and Safety Study of Benralizumab in Adults and Adolescents Inadequately Controlled on Inhaled Corticosteroid Plus Long-acting [beta]2 Agonist. A Multicentre, Randomized, Double-blind, Parallel Group, Placebocontrolled, Phase 3 Study to Evaluate the Efficacy and Safety of Benralizumab in Asthmatic Adults and Adolescents Inadequately Controlled on Inhaled Corticosteroid Plus Long-acting [beta]2 Agonist (CALIMA) #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2118	NCT01928771 (2013//) Efficacy and Safety Study of Benralizumab Added to High-dose Inhaled Corticosteroid Plus LABA in Patients With Uncontrolled Asthma. A Multicentre, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase III Efficacy and Safety Study of Benralizumab (MEDI-563) Added to High-dose Inhaled Corticosteroid Plus Long-acting [beta]2 Agonist in Patients With Uncontrolled Asthma #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2120	NCT01842607 (2013//) A Study to Determine Long-term Safety of Mepolizumab in Asthmatic Subjects. A Multi-centre, Open-label, Long-term Safety Study of Mepolizumab in Asthmatic Subjects Who Participated in theMEA115588 or MEA115575 Trials #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2122	NCT01854047 (2013//) An evaluation of dupilumab in patients with moderate to severe uncontrolled asthma. A randomized, double-blind, placebo-controlled, dose-ranging study to evaluate dupilumab in patients with moderate to severe uncontrolled asthma #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2126	NCT01928771 (2013//) Efficacy and safety study of benralizumab added to high-dose inhaled corticosteroid plus LABA in patients with uncontrolled asthma. #journal# #volume# (#issue#): #pages#. #notes#.	Duplicate
2127	NCT01947946 (2013//) Efficacy and safety study of benralizumab added to medium-dose inhaled corticosteroid plus LABA in patients with uncontrolled asthma. #journal# #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2130	Trojan TD, Andrew Bird J (2013//) Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. #journal# 132 (SUPPL.1): S48. #notes#.	Intervention/Comparator
2132	Liu Y, Zhang S, Li D-W, Jiang S-J (2013//) Efficacy of Anti-Interleukin-5 Therapy with Mepolizumab in Patients with Asthma: a Meta-Analysis of Randomized Placebo-Controlled Trials. #journal# 8 (3): #pages#. #notes#.	On topic SLR/MA/NMA
2133	Djukanovic R, Wilson SJ, Castro M, Leigh R, Sutherland ER, Canvin J, Peachey G, Ackrill J, Georgiou P, Chen C-W (2013//) Omalizumab in allergic eosinophilic asthma and lung eosinophil numbers: a 78-week randomized controlled trial. #journal# 42 (#issue#): #pages#. #notes#.	Duplicate
2135	Zielen S, Lieb A, De La Motte S, Wagner F, De Monchy J, Fuhr R, Munzu C, Koehne-Voss S, Riviere G-J, Kaiser G, Erpenbeck VJ (2013//) Omalizumab protects against allergen-induced bronchoconstriction in allergic (Immunoglobulin E-mediated) Asthma. #journal# 160 (1): 102. #notes#.	Population

2136	Ortega HG, Chupp G, Bardin P, Bourdin A, Hartley B, Humbert M (2013//) The role of mepolizumab in atopic and non-atopic patients with refractory eosinophilic asthma.. #journal# 187 (#issue#): #pages#. #notes#.	Duplicate
2137	Wenzel S, Ming J, Hamilton J, Radin A, Rocklin R, Hultsch T, Wang L, Skobieranda F, Pirozzi G (2013//) Therapeutic blockade of IL-4 and 13 signaling with dupilumab (SAR231893/REGN668) inhibits key biomarkers in asthma.. #journal# 42 (#issue#): #pages#. #notes#.	Duplicate
2138	Zakaria M, Abu-Hussein S, Abu-Hussein A, Ahmed M (2013//) The effect of omalizumab in treatment of inadequate controlled severe persistent asthma patient.. #journal# 144 (4 MEETING ABSTRACT): #pages#. #notes#.	Duplicate
2139	Zakaria M, Abu-Hussein S, Abu-Hussein A, Ahmed M (2013//) The effect of omalizumab in treatment of inadequate controlled severe persistent asthma patient [Abstract]. #journal# 144 (4 Meeting Abstracts): 76A. #notes#.	Duplicate
2140	Wenzel SE, Pirozzi G, Wang L, Kirkesseli S, Rocklin R, Radin A, et al (2013//) Efficacy and safety of SAR231893/REGN668 in patients with moderate-to-severe, persistent asthma and elevated eosinophil levels. #journal# 187 (Meeting Abstracts): A6068. #notes#.	Duplicate
2141	Turner, Stephen William, Friend, Amanda Jane, Okpapi, Augusta (2012//) Asthma and other recurrent wheezing disorders in children (chronic).. BMJ clinical evidence 2012 (#issue#): #pages#. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
2192	Pavord I.D., Korn S., Howarth P., Bleecker E.R., Buhl R., Keene O.N., Ortega H., Chanez P. (2012//) Mepolizumab for severe eosinophilic asthma (DREAM): A multicentre, double-blind, placebo-controlled trial. The Lancet 380 (9842): 651. #notes#.	Intervention/Comparator
2202	Turner S.W., Friend A.J., Okpapi A. (2012//) Asthma and other recurrent wheezing disorders in children (chronic). BMJ clinical evidence 2012 (#issue#): #pages#. #notes#.	Duplicate
2218	Gossage D.L., Laviolette M., Gauvreau G.M., Leigh R., Kolbeck R., Wu Y., Richman L., Molfino N.A. (2012//) Depletion of airway eosinophils by benralizumab an anti-IL5 receptor alpha monoclonal antibody. American Journal of Respiratory and Critical Care Medicine 185 (MeetingAbstracts): #pages#. #notes#.	Intervention/Comparator
2219	Dasgupta A., Nair P. (2012//) Sample sizes for clinical trials using sputum eosinophils as an outcome. American Journal of Respiratory and Critical Care Medicine 185 (MeetingAbstracts): #pages#. #notes#.	On topic SLR/MA/NMA
2221	Molfino N.A., Nowak R., Silverman R.A., Rowe B.H., Smithline H., Khan F., Fiening J.P., Kim K., Parker J.M. (2012//) Reduction in the number and severity of exacerbations following acute severe asthma: Results of a placebo-controlled, randomized clinical trial with benralizumab. American Journal of Respiratory and Critical Care Medicine 185 (MeetingAbstracts): #pages#. #notes#.	Intervention/Comparator
2222	Garcia G., Magnan A., Chiron R., Cecile C.-B., Berger P., Taille C., Devouassoux G., De Blay F., Couderc L.J., Didier A., O'Callaghan D., Girodet P.-O., Bourdeix I., Le Gros V., Humbert M.J.C. (2012//) A randomized-controlled trial of omalizumab in patients with severe difficult to control nonatopic asthma. American Journal of Respiratory and Critical Care Medicine 185 (MeetingAbstracts): #pages#. #notes#.	Incomplete/Insufficient/Partial data
2223	Pavord I., Korn S., Howarth P., Bleecker E., Buhl R., Keene O., Ortega H., Chanez P. (2012//) Mepolizumab (anti-IL-5) reduces exacerbations in patients with	Intervention/Comparator

	refractory eosinophilic asthma. European Respiratory Journal 40 (SUPPL. 56): #pages#. #notes#.	
2230	Garcia G., Magnan A., Chiron R., Girodet P.-O., Le Gros V., Humbert M. (2012//) A proof-of-concept randomized-controlled trial of omalizumab in patients with severe difficult to control nonatopic asthma. European Respiratory Journal 40 (SUPPL. 56): #pages#. #notes#.	Incomplete/Insufficient/Partial data
2247	Dorenbaum A., Trzaskoma B., Haselkorn T., Mink D., Chen H., Solari P. (2012//) Patient characteristics predictive ofomalizumab response in extra. Annals of Allergy, Asthma and Immunology 109 (SUPPL. 5): A54. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
2258	NCT01508936 (2012//) Study to Evaluate the Efficacy and Safety of Reslizumab Treatment in Patients With Moderate to Severe Asthma. A 16-Week, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Reslizumab (3.0 mg/kg) Treatment in Patients With Moderate to Severe Asthma #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2259	NCT01691508 (2012//) Mepolizumab Steroid-Sparing Study in Subjects With Severe Refractory Asthma. MEA115575: a Randomised, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study of Mepolizumab Adjunctive Therapy to Reduce Steroid Use in Subjects With Severe Refractory Asthma #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2260	NCT01691521 (2012//) Efficacy and Safety Study of Mepolizumab Adjunctive Therapy in Subjects With Severe Uncontrolled Refractory Asthma. MEA115588 A Randomised, Double-blind, Double-dummy, Placebo-controlled, Parallel-group, Multi-centre Study of the Efficacy and Safety of Mepolizumab Adjunctive Therapy in Subjects With Severe Uncontrolled Refractory Asthma #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2262	NCT01703312 (2012//) A Study Evaluating the Efficacy of QGE031 Compared to Omalizumab in Patients With Allergic Asthma. A Randomized, Double-blind, Placebo- and Comparator-controlled Study Evaluating the Effect of Multiple Doses of QGE031 Compared to Omalizumab in Asthma Induced by Allergen Bronchial Provocation #volume# (#issue#): #pages#. #notes#.	Population
2263	NCT01716754 (2012//) Efficacy and Safety of QGE031versus Placebo and Omalizumab in Patients Aged 18-75 Years With Asthma. A Multi-center, Randomized, Double-blind, Placebo and Active-controlled Study With Exploratory Dose-ranging to Investigate the Efficacy and Safety of 16 Weeks Treatment With Subcutaneous (s.c.) QGE031 in Asthma Patients Not Adequately Controlled With High-dose Inhaled Corticosteroids and Long Acting [beta]2-agonists #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2265	EUCTR2012-001251-40-BE (2012//) Mepolizumab for the treatment of severe asthma. MEA115588 A randomised, double-blind, double-dummy, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of mepolizumab adjunctive therapy in subjects with severe uncontrolled refractory asthma - Efficacy of Mepolizumab in Severe Asthma #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2266	EUCTR2012-002298-69-IT (2012//) Efficacy and safety of QGE031 versus placebo and Omalizumab in patients aged 18-75 years with asthma. A Multi-Center, Randomized, Double Blind, Placebo and Active-Controlled study with exploratory dose-ranging, to investigate the efficacy and safety of 16 weeks treatment with subcutaneous QGE031 in asthma patients not adequately controlled with high-dose inhaled corticosteroids and long acting [latin sharp s]2-agonists #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2267	EUCTR2012-003350-84-SE (2012//) Flora to provide confirmation: "A study evaluating the efficacy of QGE031 compared to omalizumab in patients with	Relevant clinical trial records

	allergic asthma.". A randomized, double-blind, placebo- and comparator-controlled study evaluating the effect of multiple doses of QGE031 compared to omalizumab in asthma induced by allergen bronchial provocation #volume# (#issue#): #pages#. #notes#.	
2268	EUCTR2012-001497-29-NL (2012//) A study of mepolizumab (study medication) as add-on therapy in subjects who require daily oral corticosteroids to treat their severe asthma. MEA115575: a Randomised, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study of Mepolizumab Adjunctive Therapy to Reduce Steroid Use in Subjects with Severe Refractory Asthma #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2269	NCT01508936 (2012//) A 16-week, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of reslizumab (3.0 mg/kg) treatment in patients with moderate to severe asthma. #journal# #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2270	EUCTR2012-002106-48-IE (2012//) An Investigative Study to characterize gene expression patterns in myeloid cells that are triggered during acute asthma exacerbations, and to identify associated genes/gene networks that are Omalizumab sensitive. #journal# #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2271	Garcia G, Magnan A, Chiron R, Girodet P-O, Le Gros V, Humbert M (2012//) A proof-of-concept randomized-controlled trial of omalizumab in patients with severe difficult to control nonatopic asthma. #journal# 40 (#issue#): #pages#. #notes#.	Duplicate
2272	Garcia G, Magnan A, Chiron R, Cecile C-B, Berger P, Taille C, Devouassoux G, De Blay F, Couderc LJ, Didier A, O'Callaghan D, Girodet P-O, Bourdeix I, Le Gros V, Humbert MJC (2012//) A randomized-controlled trial of omalizumab in patients with severe difficult to control nonatopic asthma. #journal# 185 (#issue#): #pages#. #notes#.	Duplicate
2273	(2012//) Omalizumab provided additional clinical benefit for patients with severe allergic asthma. #journal# 93 (1102): 76. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
2274	Garcia G, Magnan A, Chiron R, Cecile C-B, Berger P, Taille C (2012//) A Randomized-Controlled Trial Of Omalizumab In Patients With Severe Difficult To Control Nonatopic Asthma. #journal# 185 (Meeting Abstracts): A6764. #notes#.	Duplicate
2275	Molfino NA, Nowak R, Silverman RA, Rowe BH, Smithline H, Khan F (2012//) Reduction In The Number And Severity Of Exacerbations Following Acute Severe Asthma: results Of A Placebo-Controlled, Randomized Clinical Trial With Benralizumab. #journal# 185 (Meeting Abstracts): A2753. #notes#.	Duplicate
2276	Molfino NA, Nowak R, Silverman RA, Rowe BH, Smithline H, Khan F, Fiening JP, Kim K, Parker JM (2012//) Reduction in the number and severity of exacerbations following acute severe asthma: results of a placebo-controlled, randomized clinical trial with benralizumab. #journal# 185 (#issue#): #pages#. #notes#.	Duplicate
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2278	Pavord I, Korn S, Howarth P, Bleecker E, Buhl R, Keene O, Ortega H, Chanez P (2012//) Mepolizumab (anti-IL-5) reduces exacerbations in patients with refractory eosinophilic asthma.. #journal# 40 (#issue#): #pages#. #notes#.	Duplicate
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2282	Sanassi, Lorraine A (2011//) Severe persistent asthma in adults. The rise of omalizumab.. Advance for NPs & PAs 2 (5): 19. #notes#.	Unavailable
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2300	Anonymous (2011//) Omalizumab in children: a negative risk-benefit balance in severe persistent asthma.. Prescrire international 20 (115): 92. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
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2387	NCT01287039 (2011//) A Study to Evaluate the Efficacy and Safety of Reslizumab (3.0 mg/kg) in the Reduction of Clinical Asthma Exacerbations in Patients (12-75 Years of Age) With Eosinophilic Asthma. A 12-Month, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Reslizumab (3.0 mg/kg) in the Reduction of Clinical Asthma Exacerbations in Patients (12-75 Years of Age) With Eosinophilic Asthma #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2388	NCT01312961 (2011//) Efficacy, Safety, and Tolerability of Dupilumab in Patients With Persistent Moderate to Severe Eosinophilic Asthma. Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Assess the Efficacy, Safety, and Tolerability of SAR231893/REGN668 Administered Subcutaneously Once Weekly for 12 Weeks in Patients With Persistent Moderate to Severe Eosinophilic Asthma Who Are Partially Controlled/Uncontrolled by Inhaled Corticosteroid Plus Long-acting beta2 Agonist Therapy #volume# (#issue#): #pages#. #notes#.	Intervention/Comparator
2390	EUCTR2011-000586-12-NL (2011//) The efficacy of mepolizumab treatment on rhinovirus induced asthma exacerbations - MATERIAL. #journal# #volume# (#issue#): #pages#. #notes#.	Population
2391	JPRN-UMIN000005723 (2011//) A study of efficacy of humanized anti-human IgE monoclonal antibody, omalizumab for the treatment of severe nonatopic asthma. #journal# #volume# (#issue#): #pages#. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
2392	ACTRN12611001106921 (2011//) Winter-only treatment with omalizumab to prevent asthma exacerbations in children. A phase 3, multi-centre, double-blind, randomised, placebo-controlled study testing the efficacy of winter only treatment with omalizumab for the reduction of asthma exacerbations in children aged 6 to 15 years #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2393	Newbrough SA, Williams PV (2011//) Effectiveness of omalizumab in reducing corticosteroid burden in patients with moderate to severe persistent allergic asthma. #journal# 128 (SUPPL. 3): S132. #notes#.	Pooled analysis of relevant RCTs
2394	Zietkowski Z, Skiepko R, Tomasiak-Lozowska MM, Lenczewska D, Bodzenta-Lukaszyk A (2011//) RANTES in exhaled breath condensate of patients with severe persistent allergic asthma during omalizumab therapy. #journal# 154 (1): 25. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
2395	Townley R, Jourd'heuil D, Jourd'heuil F, DeMeyere-Coursey K, Mahon L, Romero T, et al (2011//) The Effects Of Omalizumab On Bronchial And Alveolar Airway Inflammation As Measured By Exhaled Nitric Oxide (ENO) In Moderate To Severe Asthmatics. #journal# 183 (1 MeetingAbstracts): A4478. #notes#.	Duplicate
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2398	Hoshino M (2011//) Effects of add-on omalizumab therapy on airway wall thickening in severe persistent asthma [Abstract]. #journal# 38 (55): 23s. #notes#.	Duplicate
2399	Yalcin AD, Kargi A, Kose S, Terzioglu E, Gorczynski RM (2011//) Efficacy of omalizumab and specific subcutaneous immunotherapy in allergic asthma.. #journal# 16 (Suppl 2): 194. #notes#.	Incomplete/Insufficient/Partial data
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2467	Condemi JJ, Hamilos DL, Hanania NA, Reyes-Rivera I, Rosen KE, Wong D, Busse W (2010//) Efficacy and safety of omalizumab in patients with moderate-to-severe persistent asthma poorly controlled on high-dose inhaled corticosteroids and long-acting beta-agonists results of a phase IIIB randomized controlled trial. #journal# 181 (1): #pages#. #notes#.	Duplicate

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2469	NCT01270464 (2010//) A Study to Evaluate the Efficacy and Safety of Reslizumab (0.3 or 3.0 mg/kg) as Treatment for Patients (12-75 Years of Age) With Eosinophilic Asthma. A 16-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Reslizumab (0.3 or 3.0 mg/kg) as Treatment for Patients (12-75 Years of Age) With Eosinophilic Asthma #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2470	NCT01238861 (2010//) Study to Evaluate the Efficacy and Safety of MEDI-563 in Adults With Uncontrolled Asthma. A Phase 2b, Dose-ranging Study to Evaluate the Efficacy and Safety of MEDI-563 in Adults With Uncontrolled Asthma #volume# (#issue#): #pages#. #notes#.	Intervention/Comparator
2471	NCT01202903 (2010//) Omalizumab in Patients With Moderate to Severe Persistent Allergic Asthma Not Adequately Controlled Despite GINA (2009) Step 4 Therapy. A 24-week, Phase III Randomized, Double-blind, Placebocontrolled, Parallel-group, Multicenter Study of Xolair(R) (Omalizumab) in Patients With Moderate to Severe Persistent Allergic Asthma Who Remain Not Adequately Controlled Despite GINA (2009) Step 4 Therapy #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2472	NCT01113437 (2010//) Omalizumab in Non-atopic Asthma. The Effect of a Humanised Monoclonal Anti-IgE Antibody,Omalizumab, on Disease Control and Bronchial Mucosal Inflammation in Non-atpic Asthma #volume# (#issue#): #pages#. #notes#.	Duplicate
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2474	NCT01238861 (2010//) Study to evaluate the efficacy and safety of MEDI-563 in adults with uncontrolled asthma. #journal# #volume# (#issue#): #pages#. #notes#.	Duplicate
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2499	Barratt, S (2009//) Mepolizumab in corticosteroid-resistant eosinophilic asthma.. Thorax 64 (6): 552. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)

2509	Nair P., Pizzichini M.M.M., Kjarsgaard M., Inman M.D., Efthimiadis A., Pizzichini E., Hargreave F.E., O'Byrne P.M. (2009//) Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. New England Journal of Medicine 360 (10): 985. #notes#.	Intervention/Comparator
2510	Haldar P., Brightling C.E., Hargadon B., Gupta S., Monteiro W., Sousa A., Marshall R.P., Bradding P., Green R.H., Wardlaw A.J., Pavord I.D. (2009//) Mepolizumab and exacerbations of refractory eosinophilic asthma. New England Journal of Medicine 360 (10): 973. #notes#.	Intervention/Comparator
2517	Panahloo Z., Casale T., Massanari M., Nelson H., Busse W., Kianifard F., Geba G., Zeldin R. (2009//) Effect of pretreatment with omalizumab with or without antihistamines on the tolerability of immunotherapy in patients with asthma inadequately controlled with inhaled corticosteroids. Allergy: European Journal of Allergy and Clinical Immunology 64 (SUPPL. 90): 344. #notes#.	Incomplete/Insufficient/Partial data
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2531	Van Rensen E.L.J., Evertse C.E., Van Schadewijk W.A.A.M., Van Wijngaarden S., Ayre G., Mauad T., Hiemstra P.S., Sterk P.J., Rabe K.F. (2009//) Eosinophils in bronchial mucosa of asthmatics after allergen challenge: Effect of anti-IgE treatment. Allergy: European Journal of Allergy and Clinical Immunology 64 (1): 72. #notes#.	Population
2532	Slavin R.G., Ferioli C., Tannenbaum S.J., Martin C., Blogg M., Lowe P.J. (2009//) Asthma symptom re-emergence after omalizumab withdrawal correlates well with increasing IgE and decreasing pharmacokinetic concentrations. Journal of Allergy and Clinical Immunology 123 (1): 107. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
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2539	Antoniu S.A. (2009//) Mepolizumab for difficult-to-control asthma with persistent sputum eosinophilia. Expert Opinion on Investigational Drugs 18 (6): 869. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
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2541	Patel B.M., Chiang D.T., Clark J.P., Romero F.A., Casale T.B. (2009//) Effects of omalizumab (Xolair) on airway hyperresponsiveness. Journal of Allergy and Clinical Immunology 123 (2 SUPPL. 1): S263. #notes#.	Incomplete/Insufficient/Partial data
2551	NCT01007149 (2009//) Effect of Omalizumab in Patients With Severe Persistent Non-atopic Uncontrolled Asthma. A 16-week Treatment, Multicenter, Randomized, Double Blind, Placebo-controlled, Parallel-group Study to Assess the Effect of Omalizumab on the Expression of Fc[epsilon]RI	Relevant clinical trial records

	Receptors of Blood Basophils and Dendritic Cells in Patients With Severe Persistent Non-atopic Asthma, Uncontrolled Despite Optimal Therapy #volume# (#issue#): #pages#. #notes#.	
2552	NCT01000506 (2009//) Dose Ranging Efficacy And Safety With Mepolizumab in Severe Asthma. A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group, Dose Ranging Study to Determine the Effect of Mepolizumab on Exacerbation Rates in Subjects With Severe Uncontrolled Refractory Asthma #volume# (#issue#): #pages#. #notes#.	Intervention/Comparator
2553	NCT01007149 (2009//) Effect of Omalizumab in Patients With Severe Persistent Non-atopic Uncontrolled Asthma (NATAIR). #journal# #volume# (#issue#): #pages#. #notes#.	Duplicate
2554	NCT00870584 (2009//) A 26-week Randomized, Double-blind, Placebo-controlled, Multi-center Study to Evaluate the Effect of Omalizumab on Markers of Asthma Impairment in Patients With Persistent Allergic Asthma. #journal# #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2555	NCT01000506 (2009//) A multicenter, randomized, double-blind, placebo-controlled, parallel group, dose ranging study to determine the effect of mepolizumab on exacerbation rates in subjects with severe uncontrolled refractory asthma. #journal# #volume# (#issue#): #pages#. #notes#.	Intervention/Comparator
2556	JPRN-UMIN000002765 (2009//) Clinical effects of treatment with omalizumab in patients with asthma. #journal# #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2557	JPRN-UMIN000002389 (2009//) Comprehensive study to examine the effects of omalizumab in patients with bronchial asthma. #journal# #volume# (#issue#): #pages#. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
2558	EUCTR2009-010937-38-FR (2009//) A 16-week treatment, multicenter, randomized, double blind, placebo-controlled, parallel-group study to assess the effect of omalizumab on the expression of FceRI receptors of blood basophils and dendritic cells in patients with severe persistent non-atopic asthma, uncontrolled despite optimal therapy. - NATAIR. #journal# #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
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2560	EUCTR2009-009154-25-GB (2009//) The effect of Omalizumab on asthma control. The effect of a humanised monoclonal anti-IgE antibody (omalizumab) on disease control and bronchial mucosal inflammation in non-atopic ("intrinsic") asthma - Omalizumab #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2561	EUCTR2009-014415-12-DE (2009//) A multicentre, randomised, double-blind, placebo-controlled, parallel group, dose ranging study to determine the effect of mepolizumab on exacerbation rates in subjects with severe uncontrolled refractory asthma. #journal# #volume# (#issue#): #pages#. #notes#.	Intervention/Comparator
2563	Gupta S, Halder P, Hargadon B, Sousa A, Marshall RP, Wardlaw AJ et al (2009//) Assessment of changes in airways dimensions with mepolizumab treatment in refractory eosinophilic asthma. #journal# #volume# (#issue#): A3641. #notes#.	Intervention/Comparator
2564	Haldar P, Brightling C, Hargadon B, Gupta S, Monteiro W, Sousa A et al (2009//) Mepolizumab (Anti-IL5) and exacerbation frequency in refractory eosinophilic asthma. #journal# #volume# (#issue#): A3638. #notes#.	Incomplete/Insufficient/Partial data
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	severe allergic (ige-mediated) asthma irrespective of lung function at baseline. #journal# #volume# (#issue#): 3281. #notes#.	
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2596	D'Amato G. (2008//) World asthma and COPD forum: Clinical trial results with omalizumab. IDrugs 11 (7): 489. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
2603	Maykut R.J., Kianifard F., Geba G.P. (2008//) Response of older patients with ige-mediated asthma to omalizumab: A pooled analysis. Journal of Asthma 45 (3): 173. #notes#.	Subgroup analysis not of interest
2605	Anonymous. (2008//) Mepolizumab: 240563, Anti-IL-5 monoclonal antibody - GlaxoSmithKline, anti-interleukin-5 monoclonal antibody - GlaxoSmithKline, SB 240563. Drugs in R and D 9 (2): 125. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
2608	NCT00768079 (2008//) A Phase 2 Study to Evaluate the Safety and Efficacy of Intravenously Administered MEDI-563. A Phase 2, Multicenter, Randomized, Double-blind, Placebocontrolled Study to Evaluate the Safety and Efficacy of Intravenously Administered MEDI-563, A Humanized Anti-interleukin-5 Receptor Alpha Monoclonal Antibody, on Asthma Control Following Acute Exacerbations in Adults #volume# (#issue#): #pages#. #notes#.	Intervention/Comparator
2609	NCT00783289 (2008//) A Phase 2a Study to Evaluate the Safety and Tolerability of MEDI-563 in Adults With Asthma. A Phase 2a, Randomized, Double-blind, Placebo-controlled, Dose-escalation Study to Evaluate the Safety and Tolerability of Multiple-dose Subcutaneous Administration of MEDI-563, a Humanized Anti-interleukin-5 Receptor Alpha Monoclonal Antibody, in Adults With Asthma #volume# (#issue#): #pages#. #notes#.	Intervention/Comparator
2610	NCT00624832 (2008//) A Study of Efficacy of New Doses of Xolair to Protect From Allergen Challenge in Groups of Asthma Patients Defined by IgE Levels. A Randomized, Double-blind, Placebo-controlled Study to Demonstrate the Efficacy of Xolair in an Allergen Bronchoprovocation Study in Asthmatic Populations Defined by Serum IgE Concentrations #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2611	NCT00659659 (2008//) A Study to Evaluate the Safety, Tolerability and Effects of MEDI-563 in Adults With Asthma. A Phase 1, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability and Effects of MEDI-563, A Humanized Anti-Interleukin-5 Receptor Alpha Monoclonal Antibody, on Airway Eosinophils in Adults With Atopic Asthma #volume# (#issue#): #pages#. #notes#.	Intervention/Comparator
2612	NCT00670930 (2008//) Efficacy of Omalizumab in Adults (18-60 Years of Age) With Moderate-Severe, Persistent Allergic Asthma, Despite Receiving Inhaled Corticosteroids and Long Acting Beta-agonists. A Randomized, Multi-center, Double-blind, Placebo-controlled, Parallel-group Trial to Explore the Effects of 78 Weeks Omalizumab Treatment Given as Add on Therapy on Markers of Airway Inflammation and Remodeling in Patients With Moderate to Severe Persistent Allergic Asthma Receiving Inhaled Corticosteroids and Long Acting Beta-agonists #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2613	NCT00691873 (2008//) Study to Evaluate the Effect of Xolair(Omalizumab) on Improving the Tolerability of Specific Immunotherapy in Patients With at Least Moderate Persistent Allergic Asthma Inadequately Controlled With Inhaled Corticosteroids. A26-wk,Randomized,Dble-Blinded,Parallel-Grp,Placebo-Controlled,Multi-Centered Study to Eval.the Effect of Xolair(Omalizumab) on Improving the Tolerability of Spec.Immunotherapy in Patients With at Least Mod. Persistent Allergic Asthma Inadequately Controlled w/Inhaled Corticosteroids #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records

2614	NCT00587288 (2008//) Efficacy and Safety Study of Reslizumab to Treat Poorly Controlled Asthma. An Efficacy and Safety Study of Reslizumab in the Treatment of Poorly Controlled Asthma in Subjects With Eosinophilic Airway Inflammation #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2615	EUCTR2008-001414-25-NL (2008//) A Phase III randomised, double-blind, placebo-controlled, parallel-group trial to evaluate efficacy and safety of tiotropium inhalation solution delivered via Respimat (R) inhaler (5 [micro]g/day) over 48 weeks as add-on controller therapy on top of usual care in patients with severe persistent asthma. #journal# #volume# (#issue#): #pages#. #notes#.	Intervention/Comparator
2616	EUCTR2008-001413-14-IT (2008//) A Phase III randomised, double-blind, placebo-controlled, parallelgroup trial to evaluate efficacy and safety of tiotropium inhalation solution delivered via Respimat inhaler (5 mcg/day) over 48 weeks as add-on controller therapy on top of usual care in patients with severe persistent asthma - ND. A Phase III randomised, double-blind, placebo-controlled, parallelgroup trial to evaluate efficacy and safety of tiotropium inhalation solution delivered via Respimat inhaler (5 mcg/day) over 48 weeks as add-on controller therapy on top of usual care in patients with severe persistent asthma - ND #volume# (#issue#): #pages#. #notes#.	Intervention/Comparator
2617	EUCTR2007-004653-29-FR (2008//) A randomized, multi-center, double-blind, placebo-controlled, parallel-group trial to explore the effects of 78 weeks omalizumab treatment as add on therapy on airway inflammation and remodeling in patients with moderate to severe IgE-mediated asthma receiving inhaled corticosteroids and long acting beta-agonists. #journal# #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2618	Noga O, Hanf G, Kunkel G, Kleine-Tebbe J (2008//) Basophil histamine release decreases during omalizumab therapy in allergic asthmatics. #journal# 146 (1): 66. #notes#.	Population
2619	Massanari M, Sacco P, Kianifard F, Maykut R, Zeldin R (2008//) Addition of omalizumab improved functional health status in patients with impaired quality of life associated with moderate to severe persistent allergic asthma. #journal# 121 (2 Suppl 1): S154. #notes#.	Subgroup analysis not of interest
2620	Maykut R, Massanari M, Kianifard F, Zeldin R (2008//) Effect of O omalizumab on asthma control and quality of life in patients with moderate severe persistent IgE-mediated asthma and allergy to house dust mite. #journal# 121 (2 Suppl 1): S157. #notes#.	Pooled analysis of relevant RCTs
2621	Massanari M, Jimenez P, Kianifard F, Maykut R, Zeldin R (2008//) The omalizumab associated decrease in peripheral blood eosinophils in moderate severe IgE mediated asthma is sustained following inhaled steroid dose reduction. #journal# #volume# (#issue#): A105. #notes#.	Unavailable
2622	Kulus M, Bridges T, Fowler-Taylor A, Blogg M, Jimenez P (2008//) A randomized controlled study of omalizumab in children with moderate to severe persistent allergic asthma. #journal# #volume# (#issue#): #pages#. #notes#.	Unavailable
2650	Liebhaber, Myron, Dyer, Zeb (2007//) Home therapy with subcutaneous anti-immunoglobulin-E antibody omalizumab in 25 patients with immunoglobulin-E-mediated (allergic) asthma.. The Journal of asthma : official journal of the Association for the Care of Asthma 44 (3): 195. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
2659	Kim H. (2007//) Modifying the allergic response in asthma. Canadian Pharmacists Journal 140 (SUPPL. 3): S11. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
2679	Sthoeger Z.M., Eliraz A., Asher I., Berkman N., Elbirt D. (2007//) The beneficial effects of Xolair (Omalizumab) as add-on therapy in patients with severe	Subgroup analysis not of interest

	persistent asthma who are inadequately controlled despite best available treatment (GINA 2002 step IV - The Israeli arm of the INNOVATE study. Israel Medical Association Journal 9 (6): 472. #notes#.	
2680	Sommerburg O. (2007//) Better quality of life by early treatment of childhood asthma. Pharmazeutische Zeitung 152 (21): 14. #notes#.	Non-English
2682	Bousquet J., Rabe K., Humbert M., Chung K.F., Berger W., Fox H., Ayre G., Chen H., Thomas K., Blogg M., Holgate S. (2007//) Predicting and evaluating response to omalizumab in patients with severe allergic asthma. Respiratory Medicine 101 (7): 1483. #notes#.	Pooled analysis of relevant RCTs
2684	Hendeles L., Sorkness C.A. (2007//) Anti-immunoglobulin E therapy with omalizumab for asthma. Annals of Pharmacotherapy 41 (9): 1397. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
2689	NCT00454051 (2007//) Effect of Omalizumab on Expression of IgE Receptors in Adults With Severe, Inadequately Controlled Allergic Asthma. Double Blind Placebo Controlled Study to Assess the Expression of IgE on Basophils and Dendritic Cells During Omalizumab Treatment #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2692	NCT00567476 (2007//) Omalizumab Use and Asthma-Related Quality of Life in Patients With Severe Persistent Allergic Asthma. A Randomized, Open-label, Multicenter Study to Evaluate the Effect of Xolair (Omalizumab) as Add-on Therapy to Inhaled Corticosteroid + Long-Acting Beta Agonist in Fixed or Flexible Dosing Compared to Isolated Inhaled Corticosteroid + Long-Acting Beta Agonist in Fixed or Flexible Dosing in the Asthma-Related Quality of Life in Patients With Severe Persistent Allergic Asthma #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2697	Zeldin R, Massanari M, Blogg M, Jimenez P, Geba G (2007//) Treatment of moderate severe asthma with omalizumab is associated with a decrease in peripheral blood eosinophils. #journal# 30 (Suppl 51): 353s. #notes#.	Unavailable
2698	Hendeles L, Khan Y, Massanari M, Spencer T, Shuster J, Chesrown S (2007//) The effect of omalizumab on airway responsiveness to adenosine in asthma patients with poor adherence to inhaled steroids. #journal# #volume# (#issue#): Poster. #notes#.	Unavailable
2699	Ohta K, Miyamoto T, Yamamoto M, Fox H, Blogg M (2007//) Omalizumab improves lung function in asthmatic smokers with severe persistent allergic asthma. #journal# #volume# (#issue#): Poster. #notes#.	Unavailable
2700	Massanari M, Maykut RJ, Kianifard F, Zeldin RK, Geba GP (2007//) Addition of omalizumab improves quality of life in moderate to severe asthmatics receiving fluticasone 500 ug/salmeterol 50ug. #journal# 119 (1 Suppl): S4. #notes#.	Subgroup analysis not of interest
2701	Milgrom H, Massanari M, Maykut RJ, Kianifard F, Zeldin RK, Geba GP (2007//) Addition of omalizumab reduces school absenteeism in children with moderate to severe persistent asthma. #journal# 119 (1 Suppl): S150. #notes#.	Subgroup analysis not of interest
2705	Nomemie, Legendre, Verpilleux, Marie-Pascale, Ballouard, Karine (2006//) [Badly controlled severe persistent asthma: an additional new treatment].. Soins; la revue de reference infirmiere #volume# (711): 19. #notes#.	Non-English
2733	Niebauer K., Dewilde S., Fox-Rushby J., Revicki D.A. (2006//) Impact of omalizumab on quality-of-life outcomes in patients with moderate-to-severe allergic asthma. Annals of Allergy, Asthma and Immunology 96 (2): 316. #notes#.	On topic SLR/MA/NMA
2736	Chipps B., Buhl R., Beeh K.-M., Fox H., Thomas K., Reisner C. (2006//) Improvement in quality of life with omalizumab in patients with severe allergic asthma. Current Medical Research and Opinion 22 (11): 2201. #notes#.	Pooled analysis of relevant RCTs

2738	Ostrom N.K. (2006//) Outpatient pharmacotherapy for pediatric asthma. Journal of Pediatrics 148 (1): 108. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
2740	Noga O., Hanf G., Brachmann I., Klucken A.C., Kleine-Tebbe J., Rosseau S., Kunkel G., Suttorp N., Seybold J. (2006//) Effect of omalizumab treatment on peripheral eosinophil and T-lymphocyte function in patients with allergic asthma. Journal of Allergy and Clinical Immunology 117 (6): 1493. #notes#.	Population
2749	NCT00314574 (2006//) A Study of Omalizumab (Xolair) in Subjects With Moderate to Severe Persistent Asthma (EXTRA). A Phase IIIb Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Xolair in Subjects With Moderate to Severe Persistent Asthma Who Are Inadequately Controlled With High-Dose Inhaled Corticosteroids and Long-Acting Beta-Agonists #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2750	NCT00377572 (2006//) Inner-City Anti-IgE Therapy for Asthma. Inner-City Anti-IgE Therapy for Asthma (ICAC-08) #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2752	NCT00401596 (2006//) A Study to Evaluate the Safety of Xolair in Moderate to Severe Persistent Asthma Patients (ALTO). A Multicenter, Randomized, Controlled, Open-Label Study to Evaluate the Safety of Xolair in Moderate to Severe Persistent Asthma Subjects Already Treated With Other Therapies (ALTO) #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2753	NCT00367016 (2006//) Immunologic Basis of Anti-IgE Therapy (Study II: on Patients With Asthma). Immunologic Basis of Anti-IgE Therapy (Study II: on Patients With Asthma) #volume# (#issue#): #pages#. #notes#.	Population
2754	NCT00329381 (2006//) A 26-wk, Randomized, Double-Blinded,Parallel-Group, Placebo-Controlled,Multi-Centered Study to Eval.the Effect of Xolair(Omalizumab)on Improving the Tolerability of Spec.Immunotherapy in Patients With at Least Mod. Persistent Allergic Asthma Inadequately Controlled with Inhaled Corticosteroids. #journal# #volume# (#issue#): #pages#. #notes#.	Population
2755	NCT00314574 (2006//) A Phase IIIb Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Xolair in Subjects With Moderate to Severe Persistent Asthma Who Are Inadequately Controlled With High-Dose Inhaled Corticosteroids and Long-Acting Beta-Agonists. #journal# #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2758	Massanari M, Zeldin R, Maykut R, Kianifard F, Geba G (2006//) Omalizumab improves lung function and treatment effectiveness in patients with moderate-severe asthma receiving fluticasone 500mcg/salmeterol 50mcg. #journal# #volume# (#issue#): A590. #notes#.	Unavailable
2759	Novartis (2006//) Multicenter study evaluating persistency of response to omalizumab during 32 weeks treatment given as add on to optimized asthma therapy in adult and adolescent patients with severe persistent allergic asthma. #journal# #volume# (#issue#): #pages#. #notes#.	Duplicate
2760	Hebert J, Rolli M, Gao J, Reisner C (2006//) Omalizumab an anti-IgE monoclonal antibody demonstrates long-term asthma control safety and tolerability in patients with severe allergic asthma. #journal# 117 (2 Suppl 1): S9. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
2762	Beeh K-M, Pereno R, Chen H, Jimenez P (2006//) Adding omalizumab to high dose ICS and LABA significantly improves quality of life in patients with severe persistent allergic asthma. #journal# 28 (Suppl 50): 440s. #notes#.	Unavailable
2766	Belliveau, Paul P (2005//) Omalizumab: a monoclonal anti-IgE antibody.. MedGenMed : Medscape general medicine 7 (1): 27. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)

2767	Anonymous (2005//) [Ray of hope for therapy of severe allergic asthma: blockade of IgE closes the treatment gap].. MMW Fortschritte der Medizin 147 (43): 52. #notes#.	Non-English
2768	Briars, Leslie A, Diaz, Anyzeila (2005//) Omalizumab: a steroid-sparing option for improving pediatric asthma management?.. Journal of pediatric health care : official publication of National Association of Pediatric Nurse Associates & Practitioners 19 (6): 386. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
2784	Buhl R. (2005//) First antibody against IgE in view. Hope for severely ill asthmatic patients. MMW Fortschritte der Medizin 147 (39): 56. #notes#.	Non-English
2788	Luskin A.T., Kosinski M., Bresnahan B.W., Ashby M., Wong D.A. (2005//) Symptom control and improved functioning: The effect of omalizumab on Asthma-Related Quality of Life (ARQL). Journal of Asthma 42 (10): 823. #notes#.	Pooled analysis of relevant RCTs
2791	Bousquet J., Cabrera P., Berkman N., Buhl R., Holgate S., Wenzel S., Fox H., Hedgecock S., Blogg M., Della Cioppa G. (2005//) The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. Allergy: European Journal of Allergy and Clinical Immunology 60 (3): 302. #notes#.	Pooled analysis of relevant RCTs
2798	NCT00264849 (2005//) Omalizumab in Adult and Adolescent Patients With Severe Persistent Allergic Asthma. A Randomized, Open Label, Parallel-group, International, Multicenter Study Evaluating Persistency of Response to Omalizumab During 32 Weeks Treatment Given as Add on to Optimized Asthma Therapy in Adult and Adolescent Patients With Severe Persistent Allergic Asthma, Who Remain Inadequately Controlled Despite GINA (2004) Step 4 Therapy #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2800	NCT00133042 (2005//) The effect of omalizumab on airway responsiveness to adenosine in patients with poorly controlled asthma. #journal# #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2802	NCT00180011 (2005//) Efficacy of Omalizumab as Add on Therapy for Minority Patients With Moderate to Severe Asthma. Efficacy of Omalizumab as Add on Therapy for Minority Patients With Moderate to Severe Asthma #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2803	NCT00226200 (2005//) Soluble CD23 Expression in Asthma Patients Treated With OMA. Soluble CD23 Expression as a Marker of Immunomodulation and CLinical Response in Asthma Patients Treated With Omalizumab #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2804	NCT00267202 (2005//) A 26-week, Randomized, Double-blind, Parallel-group, Placebo-controlled, Multi-center Study to Evaluate the Effect of Omalizumab on Improving the Tolerability of Specific Immunotherapy in Patients With at Least Moderate Persistent Allergic Asthma Inadequately Controlled With Inhaled Corticosteroids. #journal# #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2805	NCT00232050 (2005//) Study of Omalizumab in Moderate to Severe Bronchial Asthma. #journal# #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2806	EUCTR2005-001932-61-GB (2005//) Mepolizumab and exacerbation frequency in refractory eosinophilic asthma. A randomised, double blind, placebo controlled, parallel group trial. #journal# #volume# (#issue#): #pages#. #notes#.	Intervention/Comparator
2807	EUCTR2005-001099-11-DK (2005//) A randomized, open label, parallel-group, international, multicenter study evaluating persistency of response to omalizumab during 32 weeks treatment given as add on to optimized asthma therapy in adult and adolescent patients with severe persistent allergic asthma,	Relevant clinical trial records

	who remain inadequately controlled despite GINA (2004) step 4 therapy. #journal# #volume# (#issue#): #pages#. #notes#.	
2808	JPRN-JapicCTI-050143 (2005//) Long-Term Study of IGE025 in Moderate to Severe Bronchial Asthma. #journal# #volume# (#issue#): #pages#. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
2810	Bruno L, Prieto L, Gutierrez V, Colas C, Tabar AI, Perez-Frances, Uixera S (2005//) Effect of omalizumab on adenosine 5'-monophosphate responsiveness in allergic asthma. #journal# #volume# (#issue#): Abstract. #notes#.	Population
2812	Korenblat P, Levy R, Slavin R, Hedgecock S, Fox H, Surrey K, et al (2005//) Add-on omalizumab therapy significantly reduces severe asthma exacerbations and emergency visits in patients with inadequately controlled severe persistent asthma despite GINA 2002 step 4 therapy INNOVATE. #journal# #volume# (#issue#): #pages#. #notes#.	Unavailable
2813	Matz J, Melamed I, Ledford D, Hedgecock S, Fox H, Surrey K, et al (2005//) Add-on omalizumab therapy significantly improves quality of life in patients with inadequately controlled severe persistent asthma despite GINA 2002 step 4 treatment, INNOVATE. #journal# #volume# (#issue#): #pages#. #notes#.	Unavailable
2814	Milgrom H, Miller SD, Lanier BQ, Fowler-Taylor A, Chen H, Gupta N (2005//) Long-term omalizumab therapy is well tolerated in children with moderate-to-severe IgE-medicated asthma. #journal# #volume# (#issue#): B36. #notes#.	Unavailable
2815	Massanari M, Deniz Y, Lee J, Kianifard F, Blogg M, Reisner C, et al (2005//) Omalizumab improved asthma control and reduced rescue steroid bursts in moderate to severe allergic asthma. #journal# #volume# (#issue#): Abstract. #notes#.	Unavailable
2816	Chuchalin AG, Herbert J, Rolli M, Gao J, Resiner C (2005//) Long-term safety and tolerability of omalizumab an anti-IgE monocional antibody in patients with severe allergic asthma. #journal# 26 (Suppl 49): Abstract. #notes#.	Unavailable
2817	Novartis (2005//) A 26-week, randomized, double-blind, parallel-group, placebo-controlled, multi-center study to evaluate the effect of omalizumab on improving the tolerabilty of specific immunotherapy in patients with persistent allergic asthma. #journal# #volume# (#issue#): #pages#. #notes#.	Population
2820	Aumiller, Jochen (2004//) [COPD and asthma. Therapy chances wasted. Suffocation attacks are "worse than death"].. MMW Fortschritte der Medizin 146 (47): 4. #notes#.	Non-English
2826	Ladetzki-Baehs, Kathrin, Dirsch, Verena M, Vollmar, Angelika M (2004//) [On asthma and allergic reactions. Omalizumab: from IgE to anti-IgE].. Pharmazie in unserer Zeit 33 (2): 116. #notes#.	Non-English
2834	Silkoff P.E., Romero F.A., Gupta N., Townley R.G., Milgrom H. (2004//) Exhaled nitric oxide in children with asthma receiving Xolair (omalizumab), a monoclonal anti-immunoglobulin E antibody. Pediatrics 113 (4): e308. #notes#.	Population
2835	Walker S., Monteil M., Phelan K., Lasserson T.J., Walters E.H. (2004//) Anti-IgE for chronic asthma in adults and children. The Cochrane database of systematic reviews #volume# (3): CD003559. #notes#.	On topic SLR/MA/NMA
2842	Vignola A.M., Humbert M., Bousquet J., Boulet L.-P., Hedgecock S., Blogg M., Fox H., Surrey K. (2004//) Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. Allergy: European Journal of Allergy and Clinical Immunology 59 (7): 709. #notes#.	Population
2851	Davis L.A. (2004//) Omalizumab: A novel therapy for allergic asthma. Annals of Pharmacotherapy 38 (7-8): 1236. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)

2856	CIGE0250011E1 (2004//) An open-label extension to assess long-term safety and tolerability of omalizumab treatment in adolescents and adults with severe allergic asthma who participated in the 32-week core study. #journal# #volume# (#issue#): #pages#. #notes#.	Unavailable
2857	Bousquet J, Wenzel S, Holgate S, Lumry W, Freeman P, Fox H (2004//) Predicting response to omalizumab, an anti-IgE antibody, in patients with allergic asthma. #journal# 125 (4): 1378. #notes#.	Pooled analysis of relevant RCTs
2858	Korenblat PE, Hegecock S, Surrey K, Fox H (2004//) Omalizumab in patients with severe persistent allergic asthma inadequately controlled by GINA step 4 therpay. #journal# #volume# (#issue#): B37. #notes#.	Unavailable
2859	Schachter N, Israel E, Hedgecock S, Ayre G, Deniz Y (2004//) Omalizumab reduces exacerbations in patients with moderate-severe allergic asthma requiring inhlaed corticosteroids irrespective of concomitant long-acting beta2 agonist use. #journal# #volume# (#issue#): B37. #notes#.	Unavailable
2861	Bousquet J, Ayre G, Blogg M (2004//) Omalizumab added to best standard care reduces exacerbations in patients with severe persistent asthma according to GINA 2002 classification. #journal# 24 (Suppl 48): 220s. #notes#.	Unavailable
2862	Dahl R, Ayres J, Hedgecock S, Blogg M, Surrey K, Fox H (2004//) Efficacy of omalizumab, an anti-IgE antibody, in patients with concomitant moderate-severe allergic asthma and persistent allergic rhinitis. #journal# 113 (2 Suppl): S37. #notes#.	Population
2878	Walker S., Monteil M., Phelan K., Lasserson T.J., Walters E.H. (2003//) Anti-IgE for chronic asthma. Cochrane database of systematic reviews (Online) #volume# (3): CD003559. #notes#.	On topic SLR/MA/NMA
2880	Buttner C., Lun A., Splettstoesser T., Kunkel G., Renz H. (2003//) Monoclonal anti-interleukin-5 treatment suppresses eosinophil but not T-cell functions. European Respiratory Journal 21 (5): 799. #notes#.	Population
2881	Corren J., Casale T., Deniz Y., Ashby M. (2003//) Omalizumab, a recombinant humanized anti-IgE antibody, reduces asthma-related emergency room visits and hospitalizations in patients with allergic asthma. Journal of Allergy and Clinical Immunology 111 (1): 87. #notes#.	Pooled analysis of relevant RCTs
2882	Finn A., Gross G., Van Bavel J., Lee T., Windom H., Everhard F., Fowler-Taylor A., Liu J., Gupta N. (2003//) Omalizumab improves asthma-related quality of life in patients with severe allergic asthma. Journal of Allergy and Clinical Immunology 111 (2): 278. #notes#.	Population
2884	Kips J.C., O'Connor B.J., Langley S.J., Woodcock A., Kerstjens H.A.M., Postma D.S., Danzig M., Cuss F., Pauwels R.A. (2003//) Effect of SCH55700, a humanized anti-human interleukin-5 antibody, in severe persistent asthma: A pilot study. American Journal of Respiratory and Critical Care Medicine 167 (12): 1655. #notes#.	Intervention/Comparator
2885	Lanier B.Q., Corren J., Lumry W., Liu J., Fowler-Taylor A., Gupta N. (2003//) Omalizumab is effective in the long-term control of severe allergic asthma. Annals of Allergy, Asthma and Immunology 91 (2): 154. #notes#.	Population
2886	Berger W.E., Gupta N., McAlary M., Fowler-Taylor A. (2003//) Evaluation of long-term safety of the anti-IgE antibody, omalizumab, in children with allergic asthma. Annals of Allergy, Asthma and Immunology 91 (2): 182. #notes#.	Incomplete/Insufficient/Partial data
2890	Noga O., Hanf G., Kunkel G. (2003//) Immunological and clinical changes in allergic asthmatics following treatment with omalizumab. International Archives of Allergy and Immunology 131 (1): 46. #notes#.	Population

2891	NCT01691521 (2003//) MEA115588 a randomised, double-blind, double-dummy, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of mepolizumab adjunctive therapy in subjects with severe uncontrolled refractory asthma. #journal# #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2892	Menzies-Gow A, Flood-Page P, Sehmi R, Burman J, Hamid Q, Robinson DS, Kay AB, Denburg J (2003//) Anti-IL-5 (mepolizumab) therapy induces bone marrow eosinophil maturational arrest and decreases eosinophil progenitors in the bronchial mucosa of atopic asthmatics. #journal# 111 (4): 714. #notes#.	Population
2893	Novartis Pharmaceuticals (2003//) The efficacy and safety of omalizumab in patients with severe persistent asthma. #journal# #volume# (#issue#): #pages#. #notes#.	Unavailable
2894	Bousquet J, Niven R, Ayre G, Fox H, Bogg M (2003//) Efficacy of omalizumab in patients with moderate to severe allergic asthma that is poorly controlled on GINA (1998) treatment step 3 or 4. #journal# 22 (Suppl 45): Abstract. #notes#.	Unavailable
2895	Chung F, Kunkel G, Ramos S, Ayre G, Fox H, Blogg M (2003//) Anti IgE therapy with omalizumab decreases exacerbations in patients with poorly controlled moderate to severe allergic asthma. #journal# 22 (Suppl 45): Abstract. #notes#.	Unavailable
2897	Chipps B, Kim K, Korenblat P, Deniz Y, Zberg B, Caroll A (2003//) Effect of omalizumab on healthcare utilization in patients with moderate to severe allergic asthma. #journal# 111 (2 Suppl): S144. #notes#.	Incomplete/Insufficient/Partial data
2899	Chilvers E, Howes T, Izquierdo JL, Blogg M, Oshinyemi K, Ayre G, et al (2003//) Anti-IgE therapy with omalizumab Improves lung function in patients with poorly controlled allergic asthma. #journal# #volume# (#issue#): C104. #notes#.	Unavailable
2900	Howes T, Izquierdo JL, Chilvers E, Blogg M, Oshinyemi K, Ayre G, et al (2003//) Omalizumab, an anti-IgE antibody, decreases exacerbations in patients with poorly controlled allergic asthma. #journal# #volume# (#issue#): C104. #notes#.	Unavailable
2901	Anonymous (2003//) Omalizumab appears effective in patients with poorly controlled allergic asthma. #journal# 38 (4): 197. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
2902	Chung KF, Britton M, Harnest U, Ayre G, Blogg M, Fox H (2003//) Omalizumab, an anti-IgE antibody, decreases the rate of asthma deterioration-related incidents in patients with poorly controlled allergic asthma. #journal# 1 (Suppl): Abstract. #notes#.	Unavailable
2911	Buhl R., Soler M., Matz J., Townley R., O'Brien J., Noga O., Champain K., Fox H., Thirlwell J., Della Cioppa G. (2002//) Omalizumab provides long-term control in patients with moderate-to-severe allergic asthma. European Respiratory Journal 20 (1): 73. #notes#.	Population
2913	Lemanske Jr. R.F., Nayak A., McAlary M., Everhard F., Fowler-Taylor A., Gupta N. (2002//) Omalizumab improves asthma-related quality of life in children with allergic asthma. Pediatrics 110 (5): e55. #notes#.	Incomplete/Insufficient/Partial data
2915	Buhl R., Hanf G., Soler M., Bensch G., Wolfe J., Everhard F., Champain K., Fox H., Thirlwell J. (2002//) The anti-IgE antibody omalizumab improves asthma-related quality of life in patients with allergic asthma. European Respiratory Journal 20 (5): 1088. #notes#.	Population
2925	NCT00046748 (2002//) Efficacy and Safety of Omalizumab in Patients With Severe Persistent Asthma. Ph III, 28-wk, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Assess Efficacy, Safety, Tolerability of SC Omalizumab in Adults and Adolescents w/ Severe Persist. Allergic Asthma & Are Inadequately Controlled Despite GINA (2002) Step 4 Tx #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records

2926	NCT00046748 (2002//) Ph III, 28-wk, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Assess Efficacy, Safety, Tolerability of SC Omalizumab in Adults and Adolescents w/ Severe Persist. Allergic Asthma & Are Inadequately Controlled Despite GINA (2002) Step 4 Tx. #journal# #volume# (#issue#): #pages#. #notes#.	Relevant clinical trial records
2931	Milgrom H., Berger W., Nayak A., Gupta N., Pollard S., McAlary M., Taylor A.F., Rohane P. (2001//) Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). Pediatrics 108 (2): E36. #notes#.	Incomplete/Insufficient/Partial data
2936	Busse W., Corren J., Lanier B.Q., McAlary M., Fowler-Taylor A., Cioppa G.D., Van As A., Gupta N. (2001//) Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. Journal of Allergy and Clinical Immunology 108 (2): 184. #notes#.	Population
2939	Soler M., Matz J., Townley R., Buhl R., O'Brien J., Fox H., Thirlwell J., Gupta N., Della Cioppa G. (2001//) The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. European Respiratory Journal 18 (2): 254. #notes#.	Population
2943	Holgate S.T., Bousquet J., Wenzel S., Fox H., Liu J., Castellsague J. (2001//) Efficacy of omalizumab, an anti-immunoglobulin E antibody, in patients with allergic asthma at high risk of serious asthma-related morbidity and mortality. Current Medical Research and Opinion 17 (4): 233. #notes#.	On topic SLR/MA/NMA
2945	Chung F, Fox H, Thirwell J (2001//) Omalizumab (XolairA(R)) increases the number of asthma controlled days in moderate-to-severe asthma patients compared to placebo. #journal# 107 (2): S112. #notes#.	Unavailable
2947	Buhl R, Beeh KM, Bensch G, Noga O, O'Brien JA, SolA[spacing diaeresis]r M, Champion K, Fox H, Thirlwell J, Rohane P, Gupta N, Fick R, Cioppa D (2001//) Rhumab-E25 (omalizumab, XolairA(R)) treatment allows sustained reduction of the need for inhaled corticosteroids in moderate/severe allergic asthma. #journal# 107 (2): S106. #notes#.	Unavailable
2948	Corren J, Busse W, Buhl R, SolA[spacing diaeresis]r M, Fox H, Fowler Taylor A, Champain K, Everhard F, Ashby M, McAlary M, Johnson C, Fick R (2001//) Omalizumab (Xolair) decreases the risk of serious asthma exacerbations requiring hospitalization in patients with moderate-to-severe allergic asthma. #journal# 107 (5): 932. #notes#.	Unavailable
2949	Holgate S, Chuchalin A, Herbert J, Lotvall J, Chung F, Bousquet J, Kersjens H, Fox H, Thirlwell J, Della Cioppa G (2001//) Omalizumab, a novel therapy for severe allergic asthma. #journal# 18 (Suppl 33): 37s. #notes#.	Unavailable
2950	Holgate S, Chuchalin A, Herbert J, Lotvall J, Chung F, Bousquet J, Kersjens H, Everhard F, Fox H, Thrilwell J, Della Cioppa G (2001//) Omalizumab improves asthma-specific quality of life in patients with severe allergic asthma. #journal# 18 (Suppl 33): 37s. #notes#.	Unavailable
2951	Soler M, Buhl R, Bensch G, Noga O, O'Brian J, Champain K, Fox H, Thirlwell J, Rohane R, Gupta N, Flick R, Della Cioppa G (2001//) Omalizumab (xolair, (R) rhumab-e25) treatment reduces inhaled corticosteroid use in moderate/severe allergic asthma. #journal# #volume# (#issue#): D31. #notes#.	Unavailable
2952	Soler M, Buhl R, Bensch G, Noga O, O'Brian J, Champain K, et al (2001//) Omalizumab (xolair, (r) rhumab-e25) treatment reduces inhaled corticosteroid use in moderate/severe allergic asthma. #journal# #volume# (#issue#): 183. #notes#.	Unavailable
2953	Holgate S, Chuchalin A, Hebert J, Lotvall J, Chung K, Bousquet J, Kerstiens H, Fox H, Thirlwell J, Rohane P, Della Cioppa G, Omalizumab Severe Asthma Group	Unavailable

	(2001//) Omalizumab (xolair(R), rhumab-E25), a novel therapy for severe allergic asthma. #journal# 163 (5 Suppl): A812. #notes#.	
2954	Holgate ST, Chuchalin A, Herbert J, Persson G, Chung F, Bousqet J, Kerstjens H, Everhard F, Fox H, Hutchison K, Rohane P (2001//) Omalizumab (rhumab-e25) improves asthma-specific quality of life in patients with severe allergic asthma. #journal# #volume# (#issue#): D31. #notes#.	Unavailable
2955	Lanier R, Busse W, Corren J, Chervinsky P, Bernstein J, McAlary M, Cupta N, Fowler-Taylor A, Rohane P (2001//) Long-term improvement in asthma control and exacerbation frequency is achieved with omalizumab (xolair(R)) in patients with moderate-to-severe asthma. #journal# 163 (5 Suppl): A858. #notes#.	Unavailable
2956	Holgate S, Chuchalin A, Herbert J, Perrson G, Chung F, Bousquet J, Kerstiens H, Everhard F, Fox H, Hutchison K, Rohane P, 011 Asthma Study Group (2001//) Omalizumab (ruMAb-E25) improves asthma-specific quality of life in patients with severe allergic asthma. #journal# 163 (5 Suppl): A858. #notes#.	Unavailable
2961	Kips JC, O'Connor BJ, Langley SJ, Woodcock A, Kerstiens HAM, Postma DS, Danzig M, Cuss F, Pauwels RA (2000//) Results of a phase I trial with SCH55700, a humanized anti-IL-5 antibody, in severe persistent asthma. #journal# 161 (3 Suppl): A505. #notes#.	Unavailable
2962	Milgrom H., Fick Jr. R.B., Su J.Q., Reimann J.D., Bush R.K., Watrous M.L., Metzger W.J. (1999//) Treatment of allergic asthma with monoclonal anti-IgE antibody. New England Journal of Medicine 341 (26): 1966. #notes#.	Population
2963	Frew AJ (1998//) Effects of anti-IgE in asthmatic subjects. #journal# 53 Suppl 2 (#issue#): S52. #notes#.	Study design (non-RCT, opinion, commentary, single-arm, etc)
2964	Bush R, Watrous M, Miller D, Fick R, Kirchdoerfer L (1998//) rhuMAb-E25 improves quality of life (QoL) in adult patients with moderate-severe asthma. #journal# 157 (3 Suppl): A751. #notes#.	Unavailable
2965	Fahy J.V., Fleming H.E., Wong H.H., Liu J.T., Su J.Q., Reimann J., Fick Jr. R.B., Boushey H.A. (1997//) The effect of an anti-IgE monoclonal antibody on the early- and late- phase responses to allergen inhalation in asthmatic subjects. American Journal of Respiratory and Critical Care Medicine 155 (6): 1828. #notes#.	Population
2966	Boulet L.-P., Chapman K.R., Cote J., Kalra S., Bhagat R., Swystun V.A., Laviolette M., Cleland L.D., Deschesnes F., Su J.Q., Devault A., Fick Jr. R.B., Cockcroft D.W. (1997//) Inhibitory effects of an anti-IgE antibody E25 on allergen-induced early asthmatic response. American Journal of Respiratory and Critical Care Medicine 155 (6): 1835. #notes#.	Population
2969	Pike, Katharine C, Akhbari, Melika, Kneale, Dylan, Harris, Katherine M (#year#) Interventions for autumn exacerbations of asthma in children. #journal# #volume# (3): #pages#. #notes#.	Duplicate
2970	Farne, Hugo A, Wilson, Amanda, Powell, Colin, Bax, Lynne, Milan, Stephen J (#year#) Anti-IL5 therapies for asthma. #journal# #volume# (9): #pages#. #notes#.	Duplicate
2971	Normansell, Rebecca, Walker, Samantha, Milan, Stephen J, Walters, Haydn E., Nair, Parameswaran (#year#) Omalizumab for asthma in adults and children. #journal# #volume# (1): #pages#. #notes#.	Duplicate

Table 83: Summary of RCT study characteristics

Intervention	Study/Author (Year); NCT number	Phase	Study population[a]	N enrolled	Blinded	Primary comparator	Intervention details	Follow-up duration (weeks)
Tezepelumab	CASCADE; NCT03688074	2	Patients with physician diagnosed asthma, who had been receiving medium-dose or high-dose ICS based on the GINA 2020 guidelines plus at least one additional asthma controller medication	116	Double-blind	Placebo	210 mg Q4W	12
	NAVIGATOR; NCT03347279	3	Adults and adolescents with severe uncontrolled asthma	1059	Double-blind	Placebo	210 mg Q4W	64
	SOURCE; NCT03406078	3	Adults with OCS dependent asthma	150	Double-blind	Placebo	210 mg Q4W	48
	PATHWAY; NCT02054130	2b	Patients whose asthma remained uncontrolled despite treatment with LABA and medium-to-high doses of inhaled glucocorticoids Patients with severe asthma that was inadequately controlled despite treatment with medium-dose (250-500ug/day fluticasone dry powder inhaler or equivalent) ICS plus a LABA	275	Double-blind	Placebo	70 mg Q4W, 210 mg Q4W, 280 mg Q2W	NR
Mepolizumab	MUSCA; NCT02281318	3b	Patients with severe eosinophilic asthma	551	Double-blind	Placebo	100 mg Q4W	24
	MENSA; NCT01691521	3	Patients with severe eosinophilic asthma	576	Double-blind	Placebo	75 mg Q4W IV, 100 mg Q4W	40
	SIRIUS; NCT01691508	3	Patients with severe eosinophilic asthma	135	Double-blind	Placebo	100 mg Q4W	32
Dupilumab	Wechsler (2021); NCT03387852	2	Patients had physician-diagnosed asthma based on the GINA 2017 guidelines, and had been receiving medium-to-high-dose inhaled glucocorticoids in combination with a LABA	296	Double-blind	Placebo	300 mg Q2W	20
	LIBERTY ASTHMA QUEST; NCT02414854	3	Patients with uncontrolled asthma	1902	Double-blind	Placebo	200 mg Q2W, 300 mg Q2W	64
	LIBERTY ASTHMA VENTURE; NCT02528214	3	Patients with severe asthma	210	Double-blind	Placebo	300 mg Q2W	36
	Wenzel (2016); NCT01854047	2b	Patients with uncontrolled persistent asthma on medium-to-high-dose ICS plus a LABA	776	Double-blind	Placebo	200 mg Q2W, 300 mg Q2W, 200 mg Q4W, 300 mg Q4W	40
Omalizumab	Mukherjee (2019); NCT02049294	NR	Patients with confirmed asthma, atopy, who were symptomatic, with evidence of sputum eosinophils, despite high dose maintenance corticosteroid therapy	11	Double-blind	Placebo	As per body weight & IgE	32
	NCT01716754	2	Patients with uncontrolled persistent asthma on medium-to-high-dose ICS plus a LABA	471	Double-blind	Placebo	As per body weight & IgE	16
	Li (2016); NCT01202903	3	Chinese patients with moderate-to-severe allergic asthma	616	Double-blind	Placebo	As per body weight & IgE	24
	Pasha (2014)	NR	Moderate-to-severe asthma	42	Double-blind	Placebo	As per body weight & IgE	16
	Busse (2013)	NR	Atopic asthma who remained symptomatic and uncontrolled on ICS with or without other controller medications despite having normal lung function	328	Double-blind	Placebo	As per body weight & IgE	24
	NATAIR; NCT01007149	3b	Severe, persistent, non-atopic uncontrolled asthma	41	Double-blind	Placebo	As per body weight & IgE	16
	eXplore; NCT00670930	4	Patients with moderate to severe asthma with persistent symptoms and evidence of	35	Double-blind	Placebo	As per body weight & IgE	78

Intervention	Study/Author (Year); NCT number	Phase	Study population[a]	N enrolled	Blinded	Primary comparator	Intervention details	Follow-up duration (weeks)
			airway inflammation despite treatment with ICS and LABA					
	QUALITX (2012)	NR	Severe persistent uncontrolled asthma	202	Open label	ICS + LABA	As per body weight & IgE	20
	Hoshino (2012)	NR	Severe allergic asthma	30	Open label	ICS + LABA	As per body weight & IgE	16
	NCT00870584	4	Patients with inadequately controlled persistent allergic asthma	271	Double-blind	Placebo	As per body weight & IgE	24
	Bardelas (2012); NCT00267202[b]	4	Patients with inadequately controlled, persistent, allergic asthma treated with Step 4 or higher asthma maintenance therapy according to the 2007 NHLBI guidelines.	271	Double-blind	Placebo	As per body weight & IgE	NR
	EXALT	NR	Severe allergic (IgE-mediated) asthma	400	Open label	OAT	As per body weight & IgE	32
	Hanania (2011); NCT00314575	NR	Severe allergic asthma inadequately controlled with standard therapy	848	Double-blind	Placebo	As per body weight & IgE	48
	Chanez (2010); NCT00454051	4	Patients with severe persistent allergic asthma	31	Double-blind	Placebo	As per body weight & IgE	16
	Ohta (2009); NCT00232050	3	Moderate-to-severe asthma	327	Double-blind	Placebo	As per body weight & IgE	12
	NCT00567476	4	Severe persistent allergic asthma	116	Open label	ICS + LABA + SABA	As per body weight & IgE	NR
	INNOVATE	NR	Severe persistent asthma who are inadequately controlled despite best available therapy	482	Double-blind	Placebo	As per body weight & IgE	28
	Holgate (2004)	NR	Patients with severe allergic asthma requiring ≥1000 mg/day fluticasone for symptom control	246	Double-blind	Placebo	As per body weight & IgE	32
	Ayres (2004)	NR	Poorly controlled (moderate-to-severe) allergic asthma	312	Open label	BSC	As per body weight & IgE	56
Reslizumab	Corren (2016); NCT01508936	3	Patients with asthma inadequately controlled by at least a medium-dose ICS	492	Double-blind	Placebo	3.0 mg/kg Q4W	12
	Bjermer (2016); NCT01270464	3	Asthma inadequately controlled by at least a medium-dose ICS and with a blood eosinophil count ≥ 400 cells/mL	315	Double-blind	Placebo	3.0 mg/kg or 0 3 mg/kg Q4W during the treatment period	16
	Castro (2015); NCT01287039 Study 1	3	Inadequately controlled asthma with elevated blood eosinophil counts	489	Double-blind	Placebo	3.0 mg/kg	65
	Castro (2015); NCT01285323 Study 2	3	Inadequately controlled asthma with elevated blood eosinophil counts	464	Double-blind	Placebo	3.0 mg/kg	65
	Castro (2011); NCT00587288	2	Poorly controlled asthma in subjects with eosinophilic airway inflammation	106	Double-blind	Placebo	3.0 mg/kg	15
Benralizumab	ANDHI; NCT03170271	3b	Patients with uncontrolled, severe eosinophilic asthma	660	Double-blind	Placebo	30 mg Q8W	24
	SOLANA; NCT02869438	3b	Patients with severe eosinophilic asthma	233	Double-blind	Placebo	30 mg Q8W	16
	ALIZE; NCT02814643	3b	Patients aged 12–21 years receiving medium-to high-dosage ICS/LABA	103	Double-blind	Placebo	30 mg Q4W	20
	ZONDA; NCT02075255	3	Patients relying on oral glucocorticoids to manage severe asthma associated with eosinophilia	220	Double-blind	Placebo	30 mg Q8W	28
	SIROCCO; NCT01928771	3	Patients with severe, uncontrolled asthma with eosinophilia	2681	Double-blind	Placebo	30 mg Q4W, 30 mg Q8W	56

Intervention	Study/Author (Year); NCT number	Phase	Study population[a]	N enrolled	Blinded	Primary comparator	Intervention details	Follow-up duration (weeks)
	CALIMA; NCT01914757	3	Patients with severe, uncontrolled asthma and elevated blood eosinophil counts	2508	Double-blind	Placebo	30 mg Q4W, 30 mg Q8W	60

[a] Study population is reported as described in the trial
[b] Bardelas 2012 references NCT00267202; however, study and baseline characteristics align with those of NCT00870584.
Abbreviations: BSC = best standard of care; GINA = Global Initiative for Asthma; ICS = inhaled corticosteroids; IgE = immunoglobulin E; IV = intravenous; kg = kilogram; LABA = long acting β-agonist; mg = milligram; NCT = national clinical trial; NR = not reported; OAT = optimized asthma therapy; Q2W = every two weeks; Q4W = every four weeks; Q8W = every eight weeks; RCT = randomized controlled trial; SABA = short-acting β-agonist.

Table 84: Summary of extension study characteristics

Intervention	Study/Author (Year); NCT number	Phase	Study population[a]	N enrolled	Blinded	Primary comparator	Intervention details	Follow-up duration (weeks)
Dupilumab	LIBERTY ASTHMA TRAVERSE; NCT02134028	3	Participants with asthma who completed the LIBERTY ASTHMA VENTURE, LIBERTY ASTHMA QUEST, NCT01854047 (P2b), or EXPEDITION study	2282	Open label	None	300 mg Q2W	NR
Benralizumab	BORA; NCT02258542	3	Adolescent patients who completed SIROCCO/CALIMA could enter the BORA phase 3 extension trial	86	Double-blind	None	30 mg Q4W, 30 mg Q8W	NR
	MELTEMI; NCT02808819	3	Patients with severe, uncontrolled asthma who completed 16 to 40 weeks of treatment in BORA.	447	Open label	None	30 mg Q4W, 30 mg Q8W	NR

[a] Study population is reported as described in the trial

Abbreviations: N = number; NCT = national clinical trial; NR = not reported; Q2W = every two weeks; Q4W = every four weeks; Q8W = every eight weeks.

15.7 Data Extraction

Data from included clinical trials were collected using a standardized data extraction form in Microsoft® Excel (Microsoft Corporation, Seattle, US). The data extraction form was piloted using a sample of key citations and updated accordingly prior to implementation. Data extraction was performed by a single reviewer and was independently assessed for accuracy and completeness by a second reviewer. Disagreements were resolved by a third independent reviewer, as necessary. The specific data elements that were captured included: general study information (e.g., reference identification, trial name, National Clinical Trial [NCT] number, author, publication date), study characteristics (e.g., study design, RCT phase, blinding, location, analysis population), treatment design details (e.g., interventions, dosing regimen, route of administration, treatment duration, length of follow-up), baseline population characteristics (e.g., sample size, age, sex, race, weight, disease severity, treatment history), and efficacy and safety endpoints (e.g., definition of endpoints, timeframe of assessments, results). Values of interest that were reported in figures but not text were estimated using the DigitizeIt software.(63)

Outcome results were qualitatively described and ranges across studies were provided. No quantitative syntheses are performed in this report; results from the ITCs will be presented in a separate section.

Outcomes of Interest

The key outcomes identified for the purpose of this SLR were the following (most relevant for ITCs):

Reduction in annualized asthma exacerbation rate (AAER)
Reduction in exacerbations leading to hospitalization
Definitions of "hospitalization" also included emergency department/room/urgent care visits and unscheduled doctor visits in addition to hospitalization
Change from baseline in ACQ score
Change from baseline in FEV1
Reduction in the OCS dose

The number of RCTs and extension studies that reported each outcome is presented in Table 9 and Table 10, respectively.

Table 85: Number of studies reporting outcomes of interest

Outcome	Number of RCTs Reporting Outcome
Reduction in AAER	26
Reduction in exacerbations leading to hospitalization[a]	15
Change in baseline in ACQ score	26
Change from baseline in FEV_1	30
Reduction in the OCS dose	4[b]

[a] *Includes studies that defined "hospitalization" to include emergency department/room/urgent care visits and unscheduled doctor visits in addition to hospitalization.*

[b] *Only relevant for studies that assessed OCS sparing and included patients who were OCS dependent.*

Abbreviations: AAER = annual asthma exacerbation rate; ACQ = Asthma Control Questionnaire; FEV1= forced expiration volume in one second; OCS = oral corticosteroid.(33, 35, 59, 64-66)

Table 86: Number of extension studies reporting outcomes of interest

Outcome	Number of Studies Reporting Outcome
Reduction in AAER	3
Reduction in exacerbations leading to hospitalization[a]	0
Change in baseline in ACQ score	2
Change from baseline in FEV_1	2
Reduction in the OCS dose	2[b]

[a] Includes studies that defined "hospitalization" to include emergency department/room/urgent care visits and unscheduled doctor visits in addition to hospitalization.

[b] Only relevant for studies that assessed OCS sparing and included patients who were OCS dependent.

Abbreviations: AAER = annual asthma exacerbation rate; ACQ = Asthma Control Questionnaire; FEV1= forced expiration volume in one second; OCS = oral corticosteroid. Quality assessment *(33, 35, 59, 64-66)*

The NICE Quality appraisal checklist for quantitative intervention studies was used to assess the quality of reporting of the included RCTs.(67) Of the 39 included RCTs, one was only reported as a letter and four only as ClinicalTrials.gov records. As such, it was deemed that these studies did not provide enough information for quality assessment. Thus, 34 RCTs were assessed for quality of reporting as they had an associated full-text publication or CSR available. Of the 34 assessed RCTs, three studied tezepelumab (Table 11), three studied mepolizumab (Table 12), three studied

dupilumab (Table 13), 14 studied omalizumab (Table 14 and Table 15), five studied reslizumab (Table 16), and six studied benralizumab (Table 17).

Overall, there was a low or unclear risk of bias for the description of study population across the assessed trials. Among trials that reported sufficient information for assessment, there was an overall low or unclear risk of bias for methods of allocation to treatment. Four trials of omalizumab were open label, thus presenting a potential source of bias. (44, 45, 47, 54) The included trials were also found to have a low or unclear risk of bias regarding reporting of outcomes and methods used to conduct analyses. The results of the assessed trials were considered to have adequate internal validity and generalizability to the target population.

Table 87: Summary of quality assessment for tezepelumab trials

Questions	NAVIGATOR (2020); NCT03347279	SOURCE (2020); NCT03406078	PATHWAY (2017); NCT02054130
Section 1: Population			
1.1 Is the source population or source area well described?	++	++	++
1.2 Is the eligible population or area representative of the source population or area?	++	++	++
1.3 Do the selected participants or areas represent the eligible population or area?	++	++	++
Section 2: Method of allocation to intervention (or comparison)*			
2.1 Allocation to intervention (or comparison). How was selection bias minimised?	++	++	++
2.2 Were interventions (and comparisons) well described and appropriate?	++	++	++
2.3 Was the allocation concealed?	++	NA	++
2.4 Were participants or investigators blind to exposure and comparison?	++	++	++
2.5 Was the exposure to the intervention and comparison adequate?	++	+	+
2.6 Was contamination acceptably low?	+	+	++
2.7 Were other interventions similar in both groups?	++	+	++
2.8 Were all participants accounted for at study conclusion?	++	++	++
2.9.1 Did the setting reflect usual North American practice?	++	++	++
2.9.2 Did the setting reflect usual EU practice?	++	++	++
2.9.3 Did the setting reflect usual other regions practice?	NA	NA	NA
2.10.1 Did the intervention or control comparison reflect usual North American practice?	++	+	++
2.10.2 Did the intervention or control comparison reflect usual EU practice?	++	+	++
2.10.3 Did the intervention or control comparison reflect usual other regions practice?	NA	NA	NA
Section 3: Outcomes			
3.1 Were outcome measures reliable?	++	++	++
3.2 Were all outcome measurements complete?	++	++	++
3.3 Were all important outcomes assessed?	++	++	++

Questions	NAVIGATOR (2020); NCT03347279	SOURCE (2020); NCT03406078	PATHWAY (2017); NCT02054130
3.4 Were outcomes relevant?	++	++	++
3.5 Were there similar follow-up times in exposure and comparison groups?	++	++	++
3.6 Was follow-up time meaningful?	++	++	++
Section 4: Analyses			
4.1 Were exposure and comparison groups similar at baseline? If not, were these adjusted?	++	++	++
4.2 Was ITT analysis conducted?	++	++	++
4.3 Was the study sufficiently powered to detect an intervention effect (if one exists)?	++	++	+
4.4 Were the estimates of effect size given or calculable?	++	++	++
4.5 Were the analytical methods appropriate?	++	++	++
4.6 Was the precision of intervention effects given or calculable? Were they meaningful?	++	+	-
Section 5: Summary			
5.1 Are the study results internally valid (i.e. unbiased)?	++	++	++
5.2 Are the findings generalisable to the source population (i.e. externally valid)?	++	++	++

Source: National Institute for Health and Care Excellence. Methods for the development of NICE public health guidance (third edition) [updated September 26, 2012, accessed September 3, 2020]. Available from: https://www.nice.org.uk/process/pmg4/chapter/appendix-f-quality-appraisal-checklist-quantitative-intervention-studies.

Abbreviations: ITT = Intention-to-treat; NA = not applicable; NR = not reported; UK = United Kingdom.

*Questions 2.9 and 2.10 were expanded to determine if study methodology reflects clinical practice in different regions (i.e., North America and Europe), as per client request.

Table 88: Summary of quality assessment for mepolizumab trials

Questions	MUSCA (2017); NCT02281318	MENSA (2014); NCT01691521	SIRIUS (2014); NCT01691508
Section 1: Population			
1.1 Is the source population or source area well described?	++	++	++
1.2 Is the eligible population or area representative of the source population or area?	++	++	++
1.3 Do the selected participants or areas represent the eligible population or area?	++	++	++
Section 2: Method of allocation to intervention (or comparison)*			
2.1 Allocation to intervention (or comparison). How was selection bias minimised?	++	++	++
2.2 Were interventions (and comparisons) well described and appropriate?	++	++	++
2.3 Was the allocation concealed?	++	++	++
2.4 Were participants or investigators blind to exposure and comparison?	++	++	++

Questions	MUSCA (2017); NCT02281318	MENSA (2014); NCT01691521	SIRIUS (2014); NCT01691508
2.5 Was the exposure to the intervention and comparison adequate?	++	++	++
2.6 Was contamination acceptably low?	+	++	++
2.7 Were other interventions similar in both groups?	++	++	++
2.8 Were all participants accounted for at study conclusion?	++	+	++
2.9.1 Did the setting reflect usual North American practice?	++	NR	NR
2.9.2 Did the setting reflect usual EU practice?	++	NR	NR
2.9.3 Did the setting reflect usual other regions practice?	NA	NR	NR
2.10.1 Did the intervention or control comparison reflect usual North American practice?	++	++	++
2.10.2 Did the intervention or control comparison reflect usual EU practice?	++	++	++
2.10.3 Did the intervention or control comparison reflect usual other regions practice?	NA	NA	NA
Section 3: Outcomes			
3.1 Were outcome measures reliable?	++	++	++
3.2 Were all outcome measurements complete?	++	++	++
3.3 Were all important outcomes assessed?	++	++	++
3.4 Were outcomes relevant?	++	++	++
3.5 Were there similar follow-up times in exposure and comparison groups?	++	++	++
3.6 Was follow-up time meaningful?	++	++	++
Section 4: Analyses			
4.1 Were exposure and comparison groups similar at baseline? If not, were these adjusted?	++	++	++
4.2 Was ITT analysis conducted?	++	++	++
4.3 Was the study sufficiently powered to detect an intervention effect (if one exists)?	++	++	++
4.4 Were the estimates of effect size given or calculable?	++	++	++
4.5 Were the analytical methods appropriate?	+	++	++
4.6 Was the precision of intervention effects given or calculable? Were they meaningful?	++	++	++
Section 5: Summary			
5.1 Are the study results internally valid (i.e. unbiased)?	++	++	++
5.2 Are the findings generalisable to the source population (i.e. externally valid)?	++	++	++

Source: National Institute for Health and Care Excellence. Methods for the development of NICE public health guidance (third edition) [updated September 26, 2012, accessed September 3, 2020]. Available from: https://www.nice.org.uk/process/pmg4/chapter/appendix-f-quality-appraisal-checklist-quantitative-intervention-studies.

Abbreviations: ITT = Intention-to-treat; NA = not applicable; NR = not reported; UK = United Kingdom.

*Questions 2.9 and 2.10 were expanded to determine if study methodology reflects clinical practice in different regions (i.e., North America and Europe), as per client request.

Table 89: Summary of quality assessment for dupilumab trials

Questions	LIBERTY ASTHMA QUEST (2018); NCT02414854	LIBERTY ASTHMA VENTURE (2018); NCT02528214	Wenzel (2016); NCT01854047
Section 1: Population			
1.1 Is the source population or source area well described?	++	++	++
1.2 Is the eligible population or area representative of the source population or area?	++	++	++
1.3 Do the selected participants or areas represent the eligible population or area?	++	++	++
Section 2: Method of allocation to intervention (or comparison)*			
2.1 Allocation to intervention (or comparison). How was selection bias minimised?	++	++	++
2.2 Were interventions (and comparisons) well described and appropriate?	++	++	++
2.3 Was the allocation concealed?	++	++	++
2.4 Were participants or investigators blind to exposure and comparison?	++	++	++
2.5 Was the exposure to the intervention and comparison adequate?	+	++	+
2.6 Was contamination acceptably low?	++	++	++
2.7 Were other interventions similar in both groups?	++	++	++
2.8 Were all participants accounted for at study conclusion?	++	++	++
2.9.1 Did the setting reflect usual North American practice?	NR	NR	NR
2.9.2 Did the setting reflect usual EU practice?	NR	NR	NR
2.9.3 Did the setting reflect usual other regions practice?	NR	NA	NA
2.10.1 Did the intervention or control comparison reflect usual North American practice?	++	+	++
2.10.2 Did the intervention or control comparison reflect usual EU practice?	++	+	++
2.10.3 Did the intervention or control comparison reflect usual other regions practice?	NA	NA	NA
Section 3: Outcomes			
3.1 Were outcome measures reliable?	++	++	++
3.2 Were all outcome measurements complete?	++	++	++
3.3 Were all important outcomes assessed?	++	++	++
3.4 Were outcomes relevant?	++	++	++
3.5 Were there similar follow-up times in exposure and comparison groups?	++	++	++

Questions	LIBERTY ASTHMA QUEST (2018); NCT02414854	LIBERTY ASTHMA VENTURE (2018); NCT02528214	Wenzel (2016); NCT01854047
3.6 Was follow-up time meaningful?	++	++	++
Section 4: Analyses			
4.1 Were exposure and comparison groups similar at baseline? If not, were these adjusted?	+	++	+
4.2 Was ITT analysis conducted?	++	++	++
4.3 Was the study sufficiently powered to detect an intervention effect (if one exists)?	++	++	++
4.4 Were the estimates of effect size given or calculable?	++	++	++
4.5 Were the analytical methods appropriate?	++	++	++
4.6 Was the precision of intervention effects given or calculable? Were they meaningful?	++	++	+
Section 5: Summary			
5.1 Are the study results internally valid (i.e. unbiased)?	++	++	++
5.2 Are the findings generalisable to the source population (i.e. externally valid)?	++	++	++

Source: National Institute for Health and Care Excellence. Methods for the development of NICE public health guidance (third edition) [updated September 26, 2012, accessed September 3, 2020]. Available from: https://www.nice.org.uk/process/pmg4/chapter/appendix-f-quality-appraisal-checklist-quantitative-intervention-studies.

Abbreviations: ITT = Intention-to-treat; NA = not applicable; NR = not reported; UK = United Kingdom.

*Questions 2.9 and 2.10 were expanded to determine if study methodology reflects clinical practice in different regions (i.e., North America and Europe), as per client request.

Table 90: Summary of quality assessment for omalizumab trials (Part 1 of 2)

Questions	Mukherjee (2019); NCT02049294	Li (2016); NCT01202903	Pasha (2014)	NATAIR (2013); NCT01007149	QUALITX (2012)	Hoshino (2012)	Bardelas (2012); NCT00267202[a]
Section 1: Population							
1.1 Is the source population or source area well described?	++	++	++	++	++	+	+
1.2 Is the eligible population or area representative of the source population or area?	++	++	++	++	++	++	++
1.3 Do the selected participants or areas represent the eligible population or area?	++	++	++	++	++	++	++
Section 2: Method of allocation to intervention (or comparison)*							
2.1 Allocation to intervention (or comparison). How was selection bias minimised?	++	++	++	++	++	++	++
2.2 Were interventions (and comparisons) well described and appropriate?	++	++	++	++	++	++	++

Questions	Mukherjee (2019); NCT02049294	Li (2016); NCT01202903	Pasha (2014)	NATAIR (2013); NCT01007149	QUALITX (2012)	Hoshino (2012)	Bardelas (2012); NCT00267202[a]
2.3 Was the allocation concealed?	NR	++	NR	++	NR	NR	NR
2.4 Were participants or investigators blind to exposure and comparison?	++	++	++	++	-	-	++
2.5 Was the exposure to the intervention and comparison adequate?	+	++	NR	++	++	++	++
2.6 Was contamination acceptably low?	++	+	NR	++	+	++	++
2.7 Were other interventions similar in both groups?	++	++	++	++	++	++	++
2.8 Were all participants accounted for at study conclusion?	++	++	NR	++	++	++	++
2.9.1 Did the setting reflect usual North American practice?	NR	NR	NR	NR	NR	NR	NR
2.9.2 Did the setting reflect usual EU practice?	NR	NR	NR	NR	NR	NR	NR
2.9.3 Did the setting reflect usual other regions practice?	NA	NA	NA	NA	NA	NA	NA
2.10.1 Did the intervention or control comparison reflect usual North American practice?	+	++	++	++	++	++	++
2.10.2 Did the intervention or control comparison reflect usual EU practice?	+	++	++	++	++	++	++
2.10.3 Did the intervention or control comparison reflect usual other regions practice?	NA	NA	NA	NA	NA	NA	NA
Section 3: Outcomes							
3.1 Were outcome measures reliable?	++	++	++	++	++	++	++
3.2 Were all outcome measurements complete?	++	++	++	++	++	++	++
3.3 Were all important outcomes assessed?	++	++	-	+	+	+	+
3.4 Were outcomes relevant?	++	++	++	++	++	++	++
3.5 Were there similar follow-up times in exposure and comparison groups?	++	++	++	++	++	++	++
3.6 Was follow-up time meaningful?	++	++	++	++	++	++	++
Section 4: Analyses							
4.1 Were exposure and comparison groups similar at baseline? If not, were these adjusted?	+	++	++	++	++	++	++

Questions	Mukherjee (2019); NCT02049294	Li (2016); NCT01202903	Pasha (2014)	NATAIR (2013); NCT01007149	QUALITX (2012)	Hoshino (2012)	Bardelas (2012); NCT00267202[a]
4.2 Was ITT analysis conducted?	-	++	NR	++	++	+	++
4.3 Was the study sufficiently powered to detect an intervention effect (if one exists)?	-	NR	+	++	NR	NR	++
4.4 Were the estimates of effect size given or calculable?	++	++	++	++	++	++	++
4.5 Were the analytical methods appropriate?	++	++	++	++	++	++	++
4.6 Was the precision of intervention effects given or calculable? Were they meaningful?	-	++	+	+	++	++	+
Section 5: Summary							
5.1 Are the study results internally valid (i.e. unbiased)?	+	++	+	++	++	++	++
5.2 Are the findings generalisable to the source population (i.e. externally valid)?	++	++	++	++	++	++	++

Source: National Institute for Health and Care Excellence. Methods for the development of NICE public health guidance (third edition) [updated September 26, 2012, accessed September 3, 2020]. Available from: https://www.nice.org.uk/process/pmg4/chapter/appendix-f-quality-appraisal-checklist-quantitative-intervention-studies.

[a] Bardelas 2012 references NCT00267202; however, study and baseline characteristics align with those of NCT00870584.

Abbreviations: ITT = Intention-to-treat; NA = not applicable; NR = not reported; UK = United Kingdom.

*Questions 2.9 and 2.10 were expanded to determine if study methodology reflects clinical practice in different regions (i.e., North America and Europe), as per client request.

Table 91: Summary of quality assessment for omalizumab trials (Part 2 of 2)

Questions	EXALT (2011)	Hanania (2011); NCT00314575	Chanez (2010); NCT00454051	Ohta (2009); NCT00232050)	INNOVATE (2005)	Holgate (2004)	Ayres (2004)
Section 1: Population							
1.1 Is the source population or source area well described?	++	++	++	++	++	++	++
1.2 Is the eligible population or area representative of the source population or area?	++	++	++	++	++	++	++
1.3 Do the selected participants or areas represent the eligible population or area?	++	++	++	++	++	++	++
Section 2: Method of allocation to intervention (or comparison)*							
2.1 Allocation to intervention (or comparison). How was selection bias minimised?	++	++	++	++	++	++	++

Questions	EXALT (2011)	Hanania (2011); NCT00314575	Chanez (2010); NCT00454051	Ohta (2009); NCT00232050)	INNOVATE (2005)	Holgate (2004)	Ayres (2004)
2.2 Were interventions (and comparisons) well described and appropriate?	+	++	++	++	++	++	++
2.3 Was the allocation concealed?	++	++	++	++	NR	NR	NR
2.4 Were participants or investigators blind to exposure and comparison?	-	++	++	++	++	++	-
2.5 Was the exposure to the intervention and comparison adequate?	-	+	+	+	++	++	++
2.6 Was contamination acceptably low?	+	+	+	++	++	++	++
2.7 Were other interventions similar in both groups?	++	++	++	++	++	++	++
2.8 Were all participants accounted for at study conclusion?	+	+	++	++	NR	++	NR
2.9.1 Did the setting reflect usual North American practice?	NR	NR	NR	NR	NR	NR	NR
2.9.2 Did the setting reflect usual EU practice?	NR	NR	NR	NR	NR	NR	NR
2.9.3 Did the setting reflect usual other regions practice?	NR	NA	NA	NA	NA	NA	NR
2.10.1 Did the intervention or control comparison reflect usual North American practice?	++	++	++	++	++	+	++
2.10.2 Did the intervention or control comparison reflect usual EU practice?	++	++	++	++	++	+	++
2.10.3 Did the intervention or control comparison reflect usual other regions practice?	NA	NA	NA	NA	NA	NA	NA
Section 3: Outcomes							
3.1 Were outcome measures reliable?	++	++	++	++	++	++	++
3.2 Were all outcome measurements complete?	++	++	++	++	++	++	++
3.3 Were all important outcomes assessed?	++	+	-	+	+	+	+
3.4 Were outcomes relevant?	++	++	++	++	++	++	++
3.5 Were there similar follow-up times in exposure and comparison groups?	++	++	++	++	++	++	NR
3.6 Was follow-up time meaningful?	++	++	++	++	++	++	NR
Section 4: Analyses							

Questions	EXALT (2011)	Hanania (2011); NCT00314575	Chanez (2010); NCT00454051	Ohta (2009); NCT00232050)	INNOVATE (2005)	Holgate (2004)	Ayres (2004)
4.1 Were exposure and comparison groups similar at baseline? If not, were these adjusted?	++	+	+	++	++	++	++
4.2 Was ITT analysis conducted?	++	++	++	++	++	++	++
4.3 Was the study sufficiently powered to detect an intervention effect (if one exists)?	++	++	++	++	NR	++	+
4.4 Were the estimates of effect size given or calculable?	++	++	++	++	-	++	++
4.5 Were the analytical methods appropriate?	++	++	++	++	++	++	++
4.6 Was the precision of intervention effects given or calculable? Were they meaningful?	++	++	+	++	+	+	++
Section 5: Summary							
5.1 Are the study results internally valid (i.e. unbiased)?	++	++	++	++	++	++	++
5.2 Are the findings generalisable to the source population (i.e. externally valid)?	++	++	++	++	++	++	++

***Source**: National Institute for Health and Care Excellence. Methods for the development of NICE public health guidance (third edition) [updated September 26, 2012, accessed September 3, 2020]. Available from: https://www.nice.org.uk/process/pmg4/chapter/appendix-f-quality-appraisal-checklist-quantitative-intervention-studies. Abbreviations: ITT = Intention-to-treat; NA = not applicable; NR = not reported; UK = United Kingdom. *Questions 2.9 and 2.10 were expanded to determine if study methodology reflects clinical practice in different regions (i.e., North America and Europe), as per client request.*

Table 92. Summary of quality assessment for reslizumab trials

Questions	Corren (2016); NCT01508936	Bjermer (2016); NCT01270464	Castro (2015); NCT01287039	Castro (2015); NCT01285323	Castro (2011); NCT00587288
Section 1: Population					
1.1 Is the source population or source area well described?	++	++	++	++	++
1.2 Is the eligible population or area representative of the source population or area?	++	++	++	++	+
1.3 Do the selected participants or areas represent the eligible population or area?	++	++	++	++	+
Section 2: Method of allocation to intervention (or comparison)*					
2.1 Allocation to intervention (or comparison). How was selection bias minimised?	++	++	++	++	++
2.2 Were interventions (and comparisons) well described and appropriate?	++	++	++	++	++
2.3 Was the allocation concealed?	NR	NR	++	++	++

Questions	Corren (2016); NCT01508936	Bjermer (2016); NCT01270464	Castro (2015); NCT01287039	Castro (2015); NCT01285323	Castro (2011); NCT00587288
2.4 Were participants or investigators blind to exposure and comparison?	++	++	++	++	++
2.5 Was the exposure to the intervention and comparison adequate?	++	++	++	++	++
2.6 Was contamination acceptably low?	+	+	++	++	++
2.7 Were other interventions similar in both groups?	++	++	++	++	++
2.8 Were all participants accounted for at study conclusion?	++	++	+	+	++
2.9.1 Did the setting reflect usual North American practice?	NR	NR	NR	NR	NR
2.9.2 Did the setting reflect usual EU practice?	NR	NR	NR	NR	NR
2.9.3 Did the setting reflect usual other regions practice?	NA	NA	NR	NR	NR
2.10.1 Did the intervention or control comparison reflect usual North American practice?	+	+	++	++	++
2.10.2 Did the intervention or control comparison reflect usual EU practice?	+	+	++	++	++
2.10.3 Did the intervention or control comparison reflect usual other regions practice?	NA	NA	NA	NA	NA
Section 3: Outcomes					
3.1 Were outcome measures reliable?	++	++	++	++	++
3.2 Were all outcome measurements complete?	++	++	++	++	++
3.3 Were all important outcomes assessed?	+	+	++	++	+
3.4 Were outcomes relevant?	++	++	++	++	++
3.5 Were there similar follow-up times in exposure and comparison groups?	++	++	++	++	++
3.6 Was follow-up time meaningful?	++	++	++	++	++
Section 4: Analyses					
4.1 Were exposure and comparison groups similar at baseline? If not, were these adjusted?	++	++	++	++	++

Questions	Corren (2016); NCT01508936	Bjermer (2016); NCT01270464	Castro (2015); NCT01287039	Castro (2015); NCT01285323	Castro (2011); NCT00587288
4.2 Was ITT analysis conducted?	++	++	++	++	++
4.3 Was the study sufficiently powered to detect an intervention effect (if one exists)?	NR	NR	++	++	++
4.4 Were the estimates of effect size given or calculable?	++	++	++	++	++
4.5 Were the analytical methods appropriate?	++	++	++	++	++
4.6 Was the precision of intervention effects given or calculable? Were they meaningful?	+	+	++	++	++
Section 5: Summary					
5.1 Are the study results internally valid (i.e. unbiased)?	++	++	++	++	++
5.2 Are the findings generalisable to the source population (i.e. externally valid)?	++	++	++	++	+

Source: National Institute for Health and Care Excellence. Methods for the development of NICE public health guidance (third edition) [updated September 26, 2012, accessed September 3, 2020]. Available from: https://www.nice.org.uk/process/pmg4/chapter/appendix-f-quality-appraisal-checklist-quantitative-intervention-studies.

Abbreviations: ITT = Intention-to-treat; NA = not applicable; NR = not reported; UK = United Kingdom.

*Questions 2.9 and 2.10 were expanded to determine if study methodology reflects clinical practice in different regions (i.e., North America and Europe), as per client request.

Table 93: Summary of quality assessment for benralizumab trials

Questions	ANDHI (2020); NCT03170271	SOLANA (2020); NCT02869438	ALIZE (2018); NCT02814643	ZONDA (2017); NCT02075255	SIROCCO (2016); NCT01928771	CALIMA (2016); NCT01914757
Section 1: Population						
1.1 Is the source population or source area well described?	++	++	++	++	++	++
1.2 Is the eligible population or area representative of the source population or area?	++	++	-	++	++	++
1.3 Do the selected participants or areas represent the eligible population or area?	++	++	-	++	++	++
Section 2: Method of allocation to intervention (or comparison)*						

Questions	ANDHI (2020); NCT03170271	SOLANA (2020); NCT02869438	ALIZE (2018); NCT02814643	ZONDA (2017); NCT02075255	SIROCCO (2016); NCT01928771	CALIMA (2016); NCT01914757
2.1 Allocation to intervention (or comparison). How was selection bias minimised?	++	++	++	++	++	++
2.2 Were interventions (and comparisons) well described and appropriate?	++	++	++	++	++	++
2.3 Was the allocation concealed?	++	++	NR	++	++	++
2.4 Were participants or investigators blind to exposure and comparison?	++	++	++	++	++	++
2.5 Was the exposure to the intervention and comparison adequate?	++	++	++	++	++	+
2.6 Was contamination acceptably low?	++	++	++	++	++	++
2.7 Were other interventions similar in both groups?	++	++	++	++	++	++
2.8 Were all participants accounted for at study conclusion?	++	++	NR	++	+	++
2.9.1 Did the setting reflect usual North American practice?	NR	NR	NR	NR	NR	++
2.9.2 Did the setting reflect usual EU practice?	NR	NR	NR	NR	NR	++
2.9.3 Did the setting reflect usual other regions practice?	NA	NA	NA	NA	NR	NR
2.10.1 Did the intervention or control comparison reflect usual North American practice?	++	++	+	+	++	++
2.10.2 Did the intervention or control comparison reflect usual EU practice?	++	++	+	+	++	++
2.10.3 Did the intervention or control comparison reflect usual other regions practice?	NA	NA	NA	NA	NA	NA
Section 3: Outcomes						
3.1 Were outcome measures reliable?	++	++	++	++	++	++
3.2 Were all outcome measurements complete?	++	++	++	++	++	++
3.3 Were all important outcomes assessed?	++	+	+	++	++	++
3.4 Were outcomes relevant?	++	++	++	++	++	++

Questions	ANDHI (2020); NCT03170271	SOLANA (2020); NCT02869438	ALIZE (2018); NCT02814643	ZONDA (2017); NCT02075255	SIROCCO (2016); NCT01928771	CALIMA (2016); NCT01914757
3.5 Were there similar follow-up times in exposure and comparison groups?	++	++	++	++	++	++
3.6 Was follow-up time meaningful?	++	++	++	++	++	++
Section 4: Analyses						
4.1 Were exposure and comparison groups similar at baseline? If not, were these adjusted?	++	++	++	++	++	++
4.2 Was ITT analysis conducted?	++	++	++	++	++	++
4.3 Was the study sufficiently powered to detect an intervention effect (if one exists)?	++	++	NR	++	++	++
4.4 Were the estimates of effect size given or calculable?	++	++	++	++	++	++
4.5 Were the analytical methods appropriate?	++	++	++	++	++	++
4.6 Was the precision of intervention effects given or calculable? Were they meaningful?	++	+	+	++	+	+
Section 5: Summary						
5.1 Are the study results internally valid (i.e. unbiased)?	++	++	++	++	++	++
5.2 Are the findings generalisable to the source population (i.e. externally valid)?	++	++	-	++	++	++

Source: *National Institute for Health and Care Excellence. Methods for the development of NICE public health guidance (third edition) [updated September 26, 2012, accessed September 3, 2020]. Available from: https://www.nice.org.uk/process/pmg4/chapter/appendix-f-quality-appraisal-checklist-quantitative-intervention-studies.*

Abbreviations: ITT = Intention-to-treat; NA = not applicable; NR = not reported; UK = United Kingdom.

**Questions 2.9 and 2.10 were expanded to determine if study methodology reflects clinical practice in different regions (i.e., North America and Europe), as per client request.*

15.8 Unpublished data

No unpublished data has been used in the ITC of tezepelumab versus other biologics, also the NMA has been published, however not all parts are included in the publication. (68)

15.9 Ongoing studies for intervention and comparator

Table 94. Ongoing studies for tezepelumab (the search made in clinicaltrials.gov on the 19th of June 2022)

NCT number	Title	Status	Study Results	Conditions	Intervention	Characteristics
NCT04673630	Study to Evaluate the Pharmacokinetics of Tezepelumab in Children with Asthma	Recruiting	No results available	Asthma	•Biological: Tezepelumab	Study Type: Interventional Study Design: •Allocation: Non-Randomized •Intervention Model: Single Group Assignment •Masking: None (Open Label) •Primary Purpose: Basic Science Outcome Measures: •Maximum serum concentration (Cmax) •Time to reach Cmax (tmax) •Area under the concentration-time curve (AUC) •Terminal phase elimination half-life (t1/2) •Apparent clearance (CL/F) •Apparent steady-state volume of distribution (Vss/F) •Total number of subjects in the study that tested positive for anti-drug antibodies (ADA) to Tezepelumab •Related adverse events and serious adverse events in the course of treatment
NCT03927157	Study to Evaluate Tezepelumab in Adults With Severe Uncontrolled Asthma	Recruiting	No Results Available	Asthma	•Biological Tezepelumab •Other: Placebo	Study Type: Interventional Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Triple (Participant, Care Provider, Investigator) •Primary Purpose: Treatment Outcome Measures: •Annualized asthma exacerbation rate (AERR) •Change from baseline in pre-dose/prebronchodilator (pre-BD) forced expiratory volume in 1 second (FEV1)

						•Change from baseline in Standardized Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(S)+12) total score •Change from baseline in Asthma Control Questionnaire-6 (ACQ-6) Score •Change from baseline in weekly mean daily Asthma Symptom Diary score •Time to first asthma exacerbation •Change from baseline in fractional exhaled nitric oxide FENO (ppb) •Change from baseline in weekly mean rescue medication use •Asthma specific resource utilization (e.g.,eg, unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications) •Serum trough concentrations •and 6 more
NCT05274815	Study to Evaluate Efficacy and Safety of Tezepelumab in Reducing Oral Corticosteroid Use in Adult Patients With Severe Asthma	Recruiting	No Results Available	Asthma	Biological: Tezepelumab	Study Type: Interventional Study Design: •Allocation: N/A •Intervention Model: Single Group Assignment •Masking: None (Open Label) •Primary Purpose: Treatment Outcome Measures: •Proportion of participants who discontinued OCS without loss of asthma control •Proportion of participants who reduced daily prescribed maintenance OCS dose to # 5 mg/day without loss of asthma control •The Annualised Asthma Exacerbation Rate •Rate of asthma exacerbation associated with hospitalisation or emergency room (ER)

						•Rate of asthma exacerbation associated with hospitalisation •Proportion of participants who did not experience an exacerbation •Proportion of participants who did not experience an exacerbation associated with hospitalisation or ER visit •Proportion of participants who did not experience an exacerbation associated with hospitalisation •Proportion of participants with # 50% reduction from baseline in daily maintenance OCS dose •Categorised percent reduction from baseline in the daily maintenance OCS dose •and 5 more
NCT03706079	Extension Study to Evaluate the Safety and Tolerability of Tezepelumab in Adults and Adolescents With Severe, Uncontrolled Asthma	Completed	No Results Available	Asthma	•Biological: Tezepelumab •Other: Placebo	Study Type: Interventional Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Triple (Participant, Care Provider, Investigator) •Primary Purpose: Treatment Outcome Measures: •Exposure adjusted incidence rates of AEs/SAEs •Annualized asthma exacerbation rate (AAER)
NCT05329194	Effectiveness and Safety Study of Tezepelumab in Adults & Adolescent Participants With Severe Asthma in the United States	Recruiting	No Results Available	Asthma	Drug: Tezepelumab	Study Type: Interventional Study Design: •Allocation: N/A •Intervention Model: Single Group Assignment •Masking: None (Open Label) •Primary Purpose: Treatment Outcome Measures: •Annualized asthma exacerbation rate (AAER) •Proportion of participants with asthma exacerbations

						•Proportion of participants with reduced total number of asthma exacerbations •Proportion of participants with at least 50% reduction in exacerbations •Proportion of participants without an asthma exacerbation •AAER for exacerbations resulting in hospitalization, ED visit, urgent care visit •Proportion of participants with asthma exacerbations resulting in hospitalization. ED visit, or urgent care visit •Cumulative asthma exacerbation days- during hospitalization, ED visit, or urgent care •Pre-bronchodilator (pre-BD) forced expiratory volume in 1 second (FEV1) •Change from baseline in pre-bronchodilator FEV1 •and 26 more
NCT05398263	Tezepelumab Efficacy and Safety in Reducing Oral Corticosteroid Use in Adults With Oral Corticosteroid Dependent Asthma	Not yet recruiting	No Results Available	Asthma	Biological: Tezepelumab Other: Placebo	Study Type: Interventional Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Triple (Participant, Care Provider, Investigator) •Primary Purpose: Treatment Outcome Measures: •Categorised percent reduction from baseline in the daily maintenance OCS dose at Week 28 whilst maintaining asthma control. •Change from baseline in pre-bronchodilator (pre-BD) forced expiratory volume in 1 second (FEV1) at Week 28 •Proportion of subjects with 100% reduction from baseline in daily OCS dose at Week 28

						•Proportion of subjects with daily OCS dose #5 mg at Week 28 •Proportion of subjects with #50% reduction from baseline in daily OCS dose at Week 28 •Annualised asthma exacerbation rate (AAER) over 28 weeks •Time to first asthma exacerbation •Change from baseline in Asthma Control Questionnaire 6 (ACQ-6) score at Week 28 •Change from baseline in weekly mean home peak expiratory flow (PEF) (morning and evening) at Week 28 •Change from baseline in Standardized Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(s)+12) total score at Week 28 •and 6 more
NCT05280418	Tezepelumab on Airway Structure and Function in Patients With Uncontrolled Moderate-to-severe Asthma	Not yet recruiting	No Results Available	Asthma	•Biological: Tezepelumab •Biological: Placebo	Study Type: Interventional Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) •Primary Purpose: Treatment Outcome Measures: •Change in pre-bronchodilator 129Xe MRI ventilation defect percent (VDP). •Change in the post-bronchodilator 129Xe MRI ventilation defect percent (VDP). •Change in the CT mucus score (i.e. intraluminal plugging). •Change in the CT airway lumen area.

						•Change in the CT airway wall area. •Change in the CT airway wall area percentage. •Change in the CT total airway count. •Change in the CT gas trapping. •Change in the post-bronchodilator reversibility of 129Xe MRI VDP.
NCT03989544	A Study to Evaluate the Pharmacokinetics of Tezepelumab After Being Delivered by an Accessorized Pre Filled Syringe or Autoinjector Compared With Vial and Syringe in Healthy Adult Subjects	Completed	No Results Available	Asthma	•Biological: Tezepelumab	Study Type: Interventional Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment Outcome Measures: •The area under the time concentration curves from zero to infinity (AUCinf) •The maximum observed concentration (Cmax) •The areas under the time concentration curves from zero to last observation (AUClast) •Time to Cmax (tmax) •Terminal phase elimination half life (t½#z) •Apparent systemic clearance (CL/F) •Apparent terminal phase volume of distribution (Vz/F) •Presence of ADAs to tezepelumab •Number of subjects with adverse events (AEs)/ serious adverse events (SAEs)

Table 95 Ongoing studies for dupilumab (the search made in clinicaltrials.gov on the 19th of June 2022)

NCT number	Title	Status	Study Results	Conditions	Intervention	Characteristics

NCT05347771	Prevention of Asthma Exacerbations Using Dupilumab in Urban Children and Adolescents	Recruiting	No results available	Asthma	Drug: dupilumab Drug: Placebo	Study Type: Interventional Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Triple (Participant, Care Provider, Investigator) •Primary Purpose: Treatment Outcome Measures: •Number of asthma exacerbations during the 12-month treatment period •Pulmonary Function Measured by Spirometry: Forced Expiratory Volume in 1 Second (FEV1) % Predicted •Days with symptoms, nights with symptoms, and day and night albuterol use. •Asthma control measured by the Asthma Control Questionnaire-5 •Time to first asthma exacerbation •Quality of life as measured by the PROMIS Asthma Impact Short Forms (Pediatric or Parent Proxy). •Asthma burden as measured by Combined Asthma Severity Index (CASI) •Rhinitis symptoms as measured by Modified Rhinitis Symptoms Utility Index (MRSUI) •Related adverse events and serious adverse events in the course of treatment
NCT04203797	A Study to Evaluate the Effect of Dupilumab on Exercise Capacity in Adult Patients With Asthma	Recruiting	No Results Available	Asthma	Drug: dupilumab Drug: Matching placebo	Study Type: Interventional Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) •Primary Purpose: Treatment Outcome Measures:

						•Change in constant work rate exercise endurance time •Change in average number of steps walked per day •Change in total energy expenditure •Change in the mean duration of moderate-tovigorous physical activity •Change in pre- and post-exercise Forced Expiratory Volume in One Second (FEV1)
NCT03694158	Investigating Dupilumab's Effect in Asthma by Genotype	Recruiting	No Results Available	Asthma	•Drug: Dupilumab •Other: Placebo	Study Type: Interventional Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) •Primary Purpose: Treatment Outcome Measures: •The rate of asthma exacerbations •Change in pre-bronchodilator lung function •Change in CASI score
NCT05036733	Effects of Interleukin (IL)-4R-alpha Inhibition on Respiratory Microbiome and Immunologic Correlates in Severe Asthma	Recruiting	No Results Available	Asthma	Drug: dupilumab	Study Type: Interventional Study Design: •Allocation: N/A •Intervention Model: Single Group Assignment •Masking: None (Open Label) •Primary Purpose: Basic Science Outcome Measures: •Changes in alpha-diversity of respiratory microbiota •Change in beta-diversity of respiratory microbiota •Change in relative abundances of microbiota members •Change in respiratory bacterial burden

						•Changes in alpha-diversity of stool microbiota •Change in beta-diversity of stool microbiota •Forced expiratory volume (FEV1) / forced vital capacity (FVC) ratio •Forced expiratory volume (FEV1) •Change in Fractional exhaled nitric oxide (FeNO) •Asthma Control Test (ACT) •and 4 more
NCT04022447	Dupilumab for Severe Asthma in a Real-Life Setting	Completed	No Results Available	Severe Asthma	Drug: Dupilumab	Study Type: Observational Study Design: •Observational Model: Other •Time Perspective: Retrospective Outcome Measures: •asthma control with dupilumab •number of asthma exacerbations •number of asthma-related hospitalizations •FEV1 (Forced Expiratory Volume in 1 sec) •oral steroids consumption
NCT04550962	Description of Characteristics, Such as Age, Previous and Concurrent Treatments, Associated Diseases, of Patients With Asthma Treated With Dupilumab (DUPIXENT)	Recruiting	No Results Available	Asthma	Drug: Dupilumab SAR231893	Study Type: Observational Study Design: •Observational Model: Cohort •Time Perspective: Prospective Outcome Measures: •Baseline Characteristics: Socio-demographics •Baseline Characteristics: Medical history •Baseline Characteristics: Disease characteristics •Baseline Characteristics: Concomitant treatments for asthma •Dupixent and other asthma treatment use patterns •Lung function •Annualized exacerbation rate •Patient reported outcomes

						•Healthcare Resource Utilization •Number of participants with adverse events (AE) and serious adverse events (SAE)
NCT04743791	Measuring the Effect of Dupilumab Treatment on Mucociliary Clearance (MCC) in Subjects With Moderate to Severe Asthma	Not yet recruiting	No Results Available	Asthma	Drug: Dupilumab Other: Placebo	Study Type: Interventional Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) •Primary Purpose: Treatment Outcome Measures: •Change in mucociliary clearance (MCC) rate •Change in FEV1% predicted •Change in ACT score •Change in sputum eosinophils and T2 gene mean •Change in mucus plugging score by CT •Whole lung MCC90, AAC90 •Peripheral and central lung MCC90, MCC240, AAC90
NCT04502862	Dupilumab Asthma Sleep Study	Recruiting	No Results Available	Asthma	Drug: SAR231893 Drug: Placebo	Study Type: Interventional Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Triple (Participant, Care Provider, Investigator) •Primary Purpose: Treatment Outcome Measures: •Change in sleep disturbance score in Asthma Sleep Disturbance Questionnaire •Change in the number of nocturnal awakenings in Sleep Diary •Change in PROMIS sleep-related impairment assessment

						•Change in sleep quality in Sleep Diary •Change in restorative sleep in Sleep Diary •Change in WASO in Sleep Diary •Change in WASO (actigraphy data) •Change in daytime and nighttime asthma symptoms in Asthma Daytime Symptom Diary (ADSD) and Asthma Nighttime Symptom Diary (ANSD) •Change in pre-bronchodilator (BD) FEV1 •Incidence of adverse events
NCT04287621	Registry of Asthma Patients Initiating DUPIXENT®	Recruiting	No Results Available	Asthma	Drug: DUPIXENT®	Study Type: Observational Study Design: •Observational Model: Cohort •Time Perspective: Prospective Outcome Measures: •Demography •Baseline Characteristics •Baseline Treatment Characteristics •Incidence of adverse events (AEs) •Physician Assessment: - Spirometry •Physician Assessment: Fractional exhaled Nitric Oxide (FeNO) •Patient Reported Outcome: Asthma Control Questionnaire, 6-item (ACQ-6) •Patient Reported Outcome: Mini Asthma Quality of Life Questionnaire (MiniAQLQ) •Patient Reported Outcome: Global Patient Assessment •Patient Reported Outcome: Physical Activity Limitation Questionnaire (PALQ) •and 6 more

NCT03620747	Continuation of TRAVERSE-LTS12551 Evaluating Dupilumab Safety in Patients With Asthma (Long-Term Follow-Up)	Completed	No Results Available	Asthma	Drug: Dupilumab SAR231893 (REGN668)	Study Type: Interventional Study Design: •Allocation: N/A •Intervention Model: Single Group Assignment •Masking: None (Open Label) •Primary Purpose: Treatment Outcome Measures: •Treatment-emergent adverse events (TEAE) •TEAE
NCT03560466	Assessment of the Safety and Efficacy of Dupilumab in Children With Asthma (Liberty Asthma Excursion)	Active, not recruiting	No Results Available	Asthma	Drug: Dupilumab (SAR231893/ REGN668) Drug: Asthma controller therapies (incl. prednisone) Drug: Asthma reliever therapies	Study Type: Interventional Study Design: •Allocation: N/A •Intervention Model: Single Group Assignment •Masking: None (Open Label) •Primary Purpose: Treatment Outcome Measures: •The number of patients experiencing any treatment emergent adverse event (TEAE) •Japan sub-study: Change from baseline in prebronchodilator percentage (%) predicted FEV1 at Week 12 •Annualized rate of severe asthma exacerbation events during the treatment period •Change from baseline in % predicted FEV1 •Change from baseline in absolute FEV1 •Change from baseline in FVC •Change from baseline in FEF 25 to 75% •Serum dupilumab concentrations •Incidence of treatment-emergent antidrug antibodies (ADA) against dupilumab •Blood eosinophil counts •and 12 more
NCT03112577	Study of REGN3500 and	Completed	No Results Available	Asthma, Allergic	Drug: REGN3500	Study Type: Interventional

	Dupilumab in Patients With Asthma				Drug: Dupilumab Drug: Placebo Drug: Fluticasone propionate	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) •Primary Purpose: Treatment Outcome Measures: •Difference in bronchial allergen challenge (BAC)-induced changes in sputum inflammatory markers in individuals treated with REGN3500, dupilumab and the combination of REGN3500 plus dupilumab or placebo •Incidence of Treatment Emergent Adverse Events (TEAEs) •Severity of TEAEs •Serum concentration-time profile of REGN3500 •Serum concentration-time profile of REGN3500: Tmax (time at Cmax) •Serum concentration-time profile of REGN3500: AUClast (area under the curve to the last measurable concentration) •Immunogenicity of REGN3500 and dupilumab •Serum concentration of total IL-33 after single IV dose •Difference in the BAC-induced changes in sputum inflammatory mRNA signature in individual patients treated with fluticasone
NCT05097287	Study Assessing the Long-term Effect of Dupilumab on Prevention of Lung Function Decline in Adult Patients With Uncontrolled	Recruiting	No Results Available	Asthma	Drug: Dupilumab Drug: Placebo	Study Type: Interventional Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) •Primary Purpose: Treatment

	Moderate to Severe Asthma					Outcome Measures: •Rate of change from week 8 to week 52 on post-BD FEV1 slope in FeNO population •Rate of change from week 8 to week 52 on post-BD FEV1 slope in the Total population •Rate of change from week 8 to week 104 on post-BD FEV1 slope in the FeNO population •Change from baseline to week 52 in pre-BD FEV1 in FeNO and Total populations •Change from baseline to week 52 in post-BD FEV1 in FeNO and Total populations •Annualized severe exacerbation rate during the 52-week period in FeNO and Total populations •Change from baseline to week 52 in fractional exhaled nitric oxide (FeNO) levels in FeNO and Total populations •Change from baseline to week 52 in Asthma Control Questionnaire 7 items (ACQ-7) in FeNO and Total populations •Change from baseline to week 52 in pre-BD FEV1 % predicted in FeNO and Total populations •Change from baseline to week 52 in Forced Vital Capacity (FVC) in FeNO and Total populations •and 13 more
NCT03782532	Efficacy and Safety Study of Dupilumab in Patients With Persistent Asthma	Completed	No Results Available	Asthma	Drug: Dupilumab SAR231893 Drug: Placebo Drug: Asthma Controller Therapies (include prednisone) •Drug: Asthma	Study Type: Interventional Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Triple (Participant, Care Provider, Investigator) •Primary Purpose: Treatment

					Reliever Therapies	Outcome Measures: •Change in pre-bronchodilator forced expiratory volume (FEV1) •Annualized rate of severe exacerbation events •Percent change from baseline in prebronchodilator FEV1 •Annualized rate of loss of asthma control (LOAC) event •Annualized rate of severe exacerbation events resulting in hospitalization or emergency room visit •Time to first severe exacerbation event •Time to first LOAC •Change from baseline in Asthma Control Questionnaire (ACQ)-5 score •Change from baseline in ACQ-7 score •Morning/evening asthma symptom score (e-diary) •and 5 more
NCT02948959	Evaluation of Dupilumab in Children With Uncontrolled Asthma	Completed	Has Results	Asthma	Drug: Dupilumab Drug: Placebo Drug: Asthma Controller Therapies Drug: Asthma Reliever Therapies	Study Type: Interventional Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Triple (Participant, Care Provider, Investigator) •Primary Purpose: Treatment Outcome Measures: •Annualized Rate of Severe Exacerbation Events During the 52-Week Treatment Period: Baseline Blood Eosinophils >=300 Cells Per Microliter Population •Annualized Rate of Severe Exacerbation Events During the 52-Week Treatment Period: Type 2 Inflammatory Asthma Phenotype Population •Change From Baseline in Pre-bronchodilator

						Percent Predicted Forced Expiratory Volume in 1 (FEV1) Second at Week 12: Baseline Blood Eosinophils >=300 Cells Per Microliter Population •Change From Baseline in Pre-bronchodilator Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) at Week 12: Type 2 Inflammatory Asthma Phenotype Population •Change From Baseline in Asthma Control Questionnaire-Interviewer Administered, 7-question Version (ACQ-7-IA) at Week 24: Baseline Blood Eosinophils >=300 Cells Per Microliter Population •Change From Baseline in Asthma Control Questionnaire-Interviewer Administered, 7-question Version at Week 24: Type 2 Inflammatory Asthma Phenotype Population •Change From Baseline in Fractional Exhaled Nitric Oxide Level at Week 12: Baseline Blood Eosinophils >=300 Cells Per Microliter Population •Change From Baseline in Fractional Exhaled Nitric Oxide Level at Week 12: Type 2 Inflammatory Asthma Phenotype Population Change From Baseline in Pre-bronchodilator Percent Predicted Forced Expiratory Volume in 1 Second at Weeks 2, 4, 8, 24, 36 and 52: Type 2 Inflammatory Asthma Phenotype Population •Change From Baseline in Pre-bronchodilator Percent Predicted Forced Expiratory Volume in 1 Second at Weeks 2, 4, 8, 24, 36 and 52: Baseline

						Blood Eosinophils >=300 Cells Per Microliter Population •and 40 more
NCT03884842	Dupilumab on Airway Hyper-responsiveness and Ventilation Heterogeneity in Patients With Asthma.	Recruiting	No Results Available	Asthma	Biological: Dupilumab/Dupixent Biological: Placebo	Study Type: Interventional Study Design: •Allocation: Randomized •Intervention Model: Single Group Assignment •Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) •Primary Purpose: Treatment Outcome Measures: •Proportion of patients that achieve at least one doubling dose improvement in PC20 methacholine and/or a 50% reduction in FEV1 reversibility after bronchodilator. •Change in geometric mean PC20 methacholine. •Change in FEV1 reversibility. •Change in sputum eosinophil percentage (%) •Change in blood eosinophil count •Change in fraction of exhaled nitric oxide (FeNO) •Change in FEV1 (pre-bronchodilator) •Change in Asthma Control Questionnaire-5 (ACQ-5) •Change in Asthma Control Questionnaire-5 (AQLQ) •Change in Asthma Control Test
NCT04400318	The Effect of Dupilumab on Lung Function and Related Changes in Airway Volumes Detectable by Functional Respiratory Imaging in	Recruiting	No Results Available	Asthma	Drug: Dupilumab SAR231893 Drug: Placebo	Study Type: Interventional Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Triple (Participant, Care Provider, Investigator) •Primary Purpose: Treatment

	Patients With Moderate-severe Asthma					Outcome Measures: •Change from baseline to Week 24 in prebronchodilator FEV1 •Percent change from baseline to Week 24 in regional airway volumes corrected for lung volume ([s]iVaw) at total lung capacity (TLC) •Percent change from baseline to Week 24 in regional airway volumes corrected for lung volume ([s]iVaw) at functional residual capacity (FRC) •Percent change from baseline to Week 24 in regional airway resistance corrected for lung volume ([s]iRaw) at TLC •Percent change from baseline to Week 24 in regional airway resistance corrected for lung volume ([s]iVaw) at functional residual capacity (FRC) •Change from baseline to Week 24 in lobar volumes (iVlobes) at TLC •Change from baseline to Week 24 in image-based ventilation/perfusion (iV/Q) at TLC •Change from baseline to Week 24 in HRCT-based internal airflow distribution (IAD) •Change from baseline to Week 24 in FeNO •The number of patients with FeNO <25 parts per billion (ppb) at Week 24 •and 4 more
NCT05070663	A Study in Male and Female Adolescent Participants With Severe Uncontrolled Asthma Starting Treatment	Recruiting	No Results Available	Asthma		Study Type: Observational Study Design: •Observational Model: Cohort •Time Perspective: Other Outcome Measures: •Medical history (including history of asthma)

	With Dupilumab Injection (Dupixent®)					•Previous treatments for asthma •Demographic characteristics •Disease characteristics •Concomitant medication •Change from baseline to week 52 in asthma control test (ACT) score at each subsequent visit over the year of treatment •Change from baseline to week 52 in number of annualized exacerbations and description of exacerbation setting •Change from baseline to week 52 in Paediatric Asthma Quality of Life Questionnaire (PAQLQ) score •Change from baseline to week 52 in corticosteroid dose •Change from baseline to week 52 in prebronchodilator forced expiratory volume per second (FEV1) •and 9 more
NCT04998604	Evaluating treatment Reponses of Dupilumab Versus Omalizumab in Type 2 Patients	Recruiting	No Results Available	Chronic Rhinosinusitis With Nasal Polyps Asthma	•Drug: Dupilumab •Drug: Omalizumab •Drug: Placebo	Study Type: Interventional Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Triple (Participant, Investigator, Outcomes Assessor) •Primary Purpose: Treatment Outcome Measures: •Change from baseline to Week 24 in Nasal Polyp Score (NPS) •Change from baseline to Week 24 in University of Pennsylvania Smell Identification Test (UPSIT) •Change from baseline to Week 24 in the loss of smell score of the CRSwNP Nasal Symptom Diary •Change from baseline to Week 24 in the nasal congestion (NC) score of the CRSwNP Nasal Symptom Diary

						•Change from baseline to Week 24 in prebronchodilator forced expiratory volume in 1 second (FEV1) •Change from baseline to Week 24 in Total Symptom Score (TSS) derived from the CRSwNP Nasal Symptom Diary •Change from baseline to Week 24 in 22-Item Sinonasal Outcome Test (SNOT-22) and •Change from baseline to Week 24 in SNOT-22 nasal domain score •Change from baseline to Week 24 in Nasal Peak Inspiratory Flow (NPIF) •Change from baseline to Week 24 in rhinosinusitis visual analogue scale (VAS) •and 3 more
NCT05331755	Real Life Experience Survey of Dupilumab in the Netherlands	Enrolling by invitation	No Results Available	Severe Asthma	Drug: Dupilumab	Study Type: Observational Study Design: •Observational Model: Cohort •Time Perspective: Retrospective Outcome Measures: •Annual exacerbation rate •Change in lung function •Change in asthma control
NCT04173442	Post-authorization Safety Study in North America to Monitor Pregnancy and Infant Outcomes Following Administration of Dupilumab During Planned or Unexpected Pregnancy	Recruiting	No Results Available	•Atopic Dermatitis (AD) •Asthma	•Drug: dupilumab	Study Type: Observational Study Design: •Observational Model: Cohort •Time Perspective: Prospective Outcome Measures: •Rate of major structural defects •Incidence of spontaneous abortion or miscarriage •Incidence of stillbirth •Incidence of elective termination/abortion •Incidence of premature delivery •Incidence of small for gestational age

						•Incidence of a pattern of 3 or more minor structural defects •Postnatal growth deficiency •Incidence of postnatal serious or opportunistic infections in live born children •Incidence of hospitalizations in live born children
NCT04665141	Similarities and Differences of Biological Therapies for Severe Asthma.	Recruiting	No Results Available	Asthma	•Biological: Mepolizumab •Biological: Omalizumab •Biological: Reslizumab •Biological: Benralizumab •Biological: Dupilumab	Study Type: Observational Study Design: •Observational Model: Cohort •Time Perspective: Other Outcome Measures: •Treatment dose scheduling and changes of dose throughout the study. •Number of treatment discontinuations and causes of interruption throughout the study. •Incidence of Relevant Treatment-Related Adverse Events recorded throughout the study. •Severity of Treatment-Related Adverse Events recorded throughout the study. •Change of asthma control during the treatment.

Appendix B Main characteristics of included studies

Table 96 Main Characteristics of included studies (tezepelumab and dupilumab)

Trial name: NAVIGATOR	NCT number: NCT03347279
Objective	To evaluate the efficacy and safety of 210 mg Q4W tezepelumab in adults and adolescents with severe, uncontrolled asthma

Trial name: NAVIGATOR	NCT number: NCT03347279
Publications – title, author, journal, year	Menzies-Gow, Andrew et al. "Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma." The New England journal of medicine vol. 384,19 (2021): 1800-1809. doi:10.1056/NEJMoa2034975 Menzies-Gow A, et al. "a phase 3 multicentre, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy and safety of tezepelumab in adults and adolescents with severe, uncontrolled asthma." Respir Res. 2020 Oct 13;21(1):266. doi: 10.1186/s12931-020-01526-6.
Study type and design	A phase 3, multicenter, randomized, double-blind, placebo-controlled trial. First patient: November 23, 2017. Last patient: November 12, 2020
Sample size (n)	Patients (n=1061) were randomized in a 1:1 ratio to receive tezepelumab 210 mg Q4W subcutaneously (administered using a single-use vial and syringe) or placebo Q4W for 48 weeks.
Main inclusion and exclusion criteria	**Inclusion criteria:** Age 12-80 Documented physician-diagnosed asthma for at least 12 months Subjects who have received a physician-prescribed asthma controller medication with medium or high dose ICS for at least 12 months. Documented treatment with a total daily dose of either medium or high dose ICS (≥ 500 µg fluticasone propionate dry powder formulation equivalent total daily dose) for at least 3 months. At least one additional maintenance asthma controller medication is required according to standard practice of care and must be documented for at least 3 months. Morning pre-BD FEV1 <80% predicted normal (<90% for subjects 12-17 yrs) Evidence of asthma as documented by either: Documented historical reversibility of FEV1 ≥12% and ≥200 mL in the previous 12 months OR Post-BD (albuterol/salbutamol) reversibility of FEV1 ≥12% and ≥200 mL during screening. Documented history of at least 2 asthma exacerbation events within 12 months. ACQ-6 score ≥1.5 at screening and on day of randomization **Exclusion criteria:** • Pulmonary disease other than asthma. • History of cancer. • History of a clinically significant infection. • Current smokers or subjects with smoking history ≥10 pack-years and subjects using vaping products, including electronic cigarettes. • History of chronic alcohol or drug abuse within 12 months. • Hepatitis B, C or HIV. • Pregnant or breastfeeding. • History of anaphylaxis following any biologic therapy. • Subject randomized in the current study or previous tezepelumab studies

Trial name: NAVIGATOR	NCT number: NCT03347279
Intervention	Tezepelumab 210 mg Q4W subcutaneously (administered using a single-use vial and syringe). Adults (18–80 years old) and adolescents (12–17 years old) with severe, uncontrolled asthma, who are receiving treatment with medium- or high-dose inhaled corticosteroids plus at least one additional controller medication with or without oral corticosteroids (N = 1061). The study population includes approximately equal proportions of patients with high (≥ 300 cells/µL) and low (< 300 cells/µL) blood eosinophil counts. The study comprises a 5–6-week screening period, a 52-week treatment period and a 12-week post-treatment follow-up period. All patients will receive their prescribed controller medications without change throughout the study. A total of 1061 patients were randomized from 294 study sites in 18 countries; 82 of these patients were adolescents. 529 were assigned to receive tezepelumab and 532 to receive placebo Approximately 20% of the study population comprises patients who were receiving daily medium-dose ICS (fluticasone propionate 440–500 µg dry powder formulation equivalent total daily dose) plus at least one additional controller medication, with or without OCS in the 3 months before the date of informed consent. Approximately 40% of the study population comprises patients who had at least three exacerbations in the 12 months before the date of informed consent, with the remaining 60% of patients having had two exacerbations during that time period. Patients were randomized in a 1:1 ratio to receive tezepelumab 210 mg Q4W subcutaneously (administered using a single-use vial and syringe) or placebo Q4W for 48 weeks. Neither treatment will be administered at week 52.
Comparator(s)	Subcutaneously placebo Q4W
Follow-up time	52 weeks
Is the study used in the health economic model?	Yes

Primary, secondary and exploratory endpoints

Primary Outcome Measures:

Annual Asthma Exacerbation Rate in Adult and Adolescent Patients With Uncontrolled Asthma(From randomisation to Study Week 52).The annual exacerbation rate is based on unadjudicated exacerbations reported by the investigator in the eCRF. The analysis is based on the primary population (Full Analysis Set)

Annual Asthma Exacerbation Rate in Adult and Adolescent Patients With Uncontrolled Asthma in Subjects With Baseline Eosinophils < 300 Cells/uL (From randomisation to Study Week 52).The annual exacerbation rate is based on unadjudicated exacerbations reported by the investigator in the eCRF. This analysis is based on subjects with baseline eosinophils < 300 cells/uL

Secondary Outcome Measures:

1. Mean change from baseline at week 52 in Pre-dose/Pre-bronchodilator (Pre-BD) Forced Expiratory Volume in 1 Second (FEV1) (L) (Key Secondary Endpoint). Mean change from baseline in FEV1 as compared to placebo at Week 52. FEV1 is defined as the volume of air exhaled from the lungs in the first second of a forced expiration.
2. Mean change from baseline at Week 52 in standardized asthma quality of qife Questionnaire for 12 years and older (AQLQ(S)+12). Total Score (Key Secondary Endpoint) (from randomisation to Study Week 52).Mean change from baseline in AQLQ(S)+12 as compared to placebo at week 52. The AQLQ(S)+12 is a questionnaire that measures the health-related quality of life experienced by asthma subjects. The total score is defined as the average of all 32 questions in the AQLQ(S)+12 questionnaire. AQLQ(S)+12 is a 7-point scale questionnaire, ranging from 7 (no impairment) to 1 (severe impairment).
3. Mean change from baseline at week 52 in Asthma Control Questionnaire-6(ACQ-6) (Key Secondary Endpoint) (from randomisation to study week 52). Change from baseline in ACQ-6 as compared to placebo at Week 52. The ACQ-6 captures asthma symptoms and short-acting β2-agonist use via subject-report. Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The ACQ-6 score is the mean of the responses.
4. Mean change from baseline at Week 52 in Asthma Symptom Diary (Key Secondary Endpoint)(from randomisation to study Week 52). Mean change from baseline at Week 52 in Asthma Symptom Diary. The Asthma Symptom Diary comprises of 10 items (5 items in the morning; 5 items in the evening). Asthma symptoms during night time and daytime are recorded by the patient each morning and evening in the daily diary. A daily ASD score is the mean of the 10 items. Responses for all 10 items are required to calculate the daily ASD score; otherwise, it is treated as missing. For the 7-day average asthma symptom score, scoring is done with no imputation using the mean of at least 4 of the 7 daily ASD scores as a mean weekly item score. The 7-day average ASD score ranges from 0 to 4, where 0 indicates no asthma symptoms.
5. Time to First Asthma Exacerbation. Time to first occurrence of asthma exacerbation post-randomisation, presented as number of subjects with at least one asthma exacerbation as reported by the investigator in the eCRF.
6. Mean Change From Baseline at Week 52 in Clinic Fractional Exhaled Nitric Oxide (FeNO) (Ppb). Mean change from baseline at Study Week 52 in FeNO (ppb) measured at site
7. Mean Change From Baseline in Daily Rescue Medication Use (Weekly Means) at Week 52 [Time Frame: From randomisation to Study Week 52] Daily rescue medication use is defined as: Number of night inhaler puffs + 2 x [number of night nebulizer times] + number of daytime inhaler puffs + 2 x [number of day nebulizer times]. Weekly means are calculated using at least 4 of 7 days of daily rescue medication use.

8. Mean Change From Baseline in Work Productivity Loss Due to Asthma at Week 52. WPAI+CIQ (Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire) contains 10 questions. Work productivity loss is derived by sum of percentage of missed work due to asthma and product of percentage of actual working hours times degree of asthma affecting work productivity while working. Percentage of missed work due to asthma is calculated by number of hours missed work due to asthma divided by total number of hours missed work plus number of hours worked.
9. Mean Change From Baseline in Class Productivity Loss Due to Asthma at Week 52 [Time Frame: From randomisation to Study Week 52]WPAI+CIQ (Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire) contains 10 questions. Class productivity loss is derived by sum of percentage of missed class hours due to asthma and product of percentage of actual hours in class times degree of asthma affecting productivity while in class. Percentage of missed hours in class due to asthma is calculated by number of hours in class missed due to asthma divided by total number of hours in class missed plus number of hours actually in class.
10. Activity Impairment at Week 52 [Time Frame: From randomisation to Study Week 52] WPAI+CIQ (Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire) contains 10 questions. Activity impairment is the degree health affected regular activities (other than work or class) rated from 0 to 10, with 0 meaning no effect, divided by 10, and then expressed as a percentage.
11. Pharmacokinetics of Tezepelumab [Time Frame: Pre-dose samples at Baseline, Week 4, Week 12, Week 24, Week 36, Week 52, Week 64] Mean serum trough PK concentrations taken pre-dose at each visit
12. Mean Change From Baseline at Week 52 in EQ-5D-5L VAS.
13. Mean change from baseline at Study Week 52 in EQ-5D-5L VAS. EQ-5D-5L visual analogue scale (VAS) allows subjects to rate current health status on a scale of 0-100, with 0 being the worst imaginable health state.
14. Clinicians Global Impression of Change at Week 52. CGIC (Clinical global impression of change) is an overall evaluation of response to treatment, conducted by investigator using 7-point rating scale, ranging from 1 (very much improved), to 7 (very much worse)
15. Patients Global Impression of Change at Week 52. PGIC (Patient global impression of change) is an overall evaluation of response to treatment, conducted by the patient using 7-point rating scale, ranging from 1 (very much improved), to 7 (very much worse).
16. Patients Global Impression of Severity at Week 52 [Time Frame: At Study Week 52] PGI-S (Patient global impression of severity) is an overall evaluation of patient's perception of overall symptom severity using a 6-point rating scale, ranging from 0 = No symptoms, 1=Very mild symptoms, 2=Mild symptoms, 3=Moderate symptoms, 4=Severe symptoms, 5=Very severe symptoms
17. Mean Change From Baseline at Week 52 in Blood Eosinophils (Cells/uL). Mean change from baseline at Study Week 52 in blood eosinophils (cells/uL)
18. Mean Change From Baseline at Week 52 in Total Serum IgE (IU/mL). Mean change from baseline at Study Week 52 in total serum IgE (IU/mL)
19. Number of Participants With Asthma Specific Healthcare Utilization over 52 weeks Number of participants with asthma specific healthcare utilizations (e.g. unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications) over 52 weeks.
20. Mean Change From Baseline in Home Based Morning Peak Expiratory Flow (PEF) at week 52 (Weekly Means). Mean change from baseline in home based morning PEF (L/min) at Study Week 52. Home PEF testing will be performed by the subject in the morning upon awakening and in the evening at bedtime using an electronic, hand-

held spirometer. Weekly means are calculated using at least 4 of the 7 days of PEF data.

21. Mean Change From Baseline in Home Based Evening Peak Expiratory Flow (PEF) at Week 52 (Weekly Means). Mean change from baseline in home based evening PEF (L/min) at Study Week 52. Home PEF testing will be performed by the subject in the morning upon awakening and in the evening at bedtime using an electronic, hand-held spirometer. Weekly means are calculated using at least 4 of the 7 days of PEF data.
22. Mean Change From Baseline in Night Time Awakenings (Weekly Means) at Week 52. Mean change from baseline in night time awakenings due to asthma at Study Week 52. Night-time awakenings percentage defined as number of nights with awakenings due to asthma and requiring rescue medication divided by number of nights with data and multiplied by 100%. At least 4 out of 7 days of data is required to calculate a weekly mean.
23. Immunogenecity of Tezepelumab(baseline, and from time of first dose at Week 0 to end of study at Week 64). Anti-drug antibodies (ADA) responses at baseline and post baseline. Persistently positive is defined as positive at >=2 post baseline assessments (with >=16 weeks between the first and the last positive) or positive at last post baseline assessment. Transiently positive is defined as having at least one post baseline ADA positive assessment and not fulfilling the conditions of persistently positive. Treatment boosted ADA defined as baseline positive ADA that was boosted to a 4 fold or higher level following treatment. Treatment emergent ADA defined as sum of treatment induced ADA and treatment boosted ADA.
24. Proportion of Subjects Who Had no Asthma Exacerbations. The proportion of subjects who have no exacerbations is presented as the percentage of subjects with no exacerbations. This is defined as subjects who meet both the following criteria: (1) completed the 52 week treatment period and (2) did not report an exacerbation during this period.
25. Annual Asthma Exacerbation Rate Resulting in emergency room visit or hospitalisation.The annualized exacerbation rate is based on exacerbations reported by the investigator that are associated with an emergency room visit, urgent care visit, or a hospitalization (where urgent care visit was captured as an emergency room visit on the eCRF)
26. Proportion of Subjects With at Least One Asthma Exacerbation Associated with emergency room visit or hospitalisation.
27. Proportion of subjects with at least one asthma exacerbation associated with emergency room visit or hospitalisation as recorded by the investigator in the CRF. This is presented as percentage of subjects with at least one asthma exacerbation associated with emergency room visit or hospitalisation.
28. Proportion of subjects Who Had no Asthma Exacerbations Associated with Emergency room or hospitalisation. The proportion of subjects with no exacerbations is presented as percentage of subjects who meet both the following criteria: (1) completed the 52 week treatment period and (2) did not report an exacerbation associated with emergency room or hospitalisation during this period.

Trial name: NAVIGATOR	NCT number: NCT03347279
Method of analysis	• A hierarchical testing strategy was used. To assess the primary efficacy objective across a broad population of patients, the subgroup of patients with baseline EOS <300 cells/µL was included in the multiple testing procedure • Primary and secondary analyses conducted based on the FAS • Primary endpoint analysis conducted using a negative binomial regression model, with treatment group, region, age and history of exacerbations as covariates • There was >99% power to detect an AAER reduction of 50% at a two-sided significance level of 1%. For AAER in patients with blood EOS <300 cells/µL, there was 94% power to detect a rate reduction of 50% at a two-sided significance of 5%.
Subgroup analyses	In addition to the overall population, the primary objective will be assessed in a subgroup of patients with blood eosinophil counts less than 300 cells/µL.
Other relevant information	

Trial name: PATHWAY	NCT number: NCT02054130
Objective	To evaluate the efficacy and safety of three dosing regimens of tezepelumab (70 mg Q4W, 210 mg Q4W and 280 mg Q2W) in adult patients with inadequately controlled, severe asthma.
Publications – title, author, journal, year	Corren, Jonathan et al. "Tezepelumab in Adults with Uncontrolled Asthma." The New England journal of medicine vol. 377,10 (2017): 936-946. doi:10.1056/NEJMoa1704064
Study type and design	Phase 2, randomized (1:1:1:1 tezepelumab and matching PBO), double-blind, placebo-controlled trial.
Sample size (n)	584

Trial name: PATHWAY	NCT number: NCT02054130
Main inclusion and exclusion criteria	**Inclusion criteria:** • Age 18 through 75 • Body mass index (BMI) between 18-40 kg/m2 and weight greater than or equal 40 kg • Documented physician-diagnosed asthma - Subjects must have received a physician-prescribed asthma controller regimen with medium- or high-dose inhaled corticosteroids (ICS) plus long acting β2 agonist (LABA) • If on asthma controller medications in addition to ICS plus LABA, the dose of the other asthma controller medications (leukotriene receptor inhibitors, theophylline, secondary ICS, long-acting anti-muscarinics (LAMA), cromones, or maintenance oral prednisone or equivalent up to a maximum of 10 mg daily or 20 mg every other day for the maintenance treatment of asthma) must be stable. • Subjects must have a documented history of at least 2 asthma exacerbation events OR at least 1 severe asthma exacerbation resulting in hospitalization within the 12 months prior to first study visit. **Exclusion criteria:** • Diagnosis of vocal cord dysfunction, reactive airways dysfunction syndrome, hyperventilation and panic attacks, or other mimics of asthma. • Current smokers or subjects with a smoking history of ≥ 10 pack years • Former smokers with < 10 pack years must have stopped for at least 1 year to be eligible. • Any concomitant respiratory disease that in the opinion of the investigator and/or medical monitor will interfere with the evaluation of the investigational product or interpretation of subject safety or study results (eg, chronic obstructive pulmonary disease, cystic fibrosis, pulmonary fibrosis, bronchiectasis, allergic bronchopulmonary aspergillosis, Churg-Strauss syndrome). • Evidence of active liver disease. • History of Cancer, except for basal cell carcinoma or insitu carcinoma of the cervix treated with apparent success with curative therapy or other malignancies are eligible provided that curative therapy was completed -Known history of active tuberculosis (TB) • History of anaphylaxis to any biologic therapy • Positive medical history for hepatitis B or C • Subject with human immunodeficiency virus (HIV) or subject taking antiretroviral medications, as determined by medical history and/or subject's verbal report.
Intervention	ITT: 550 patients (patients who were randomised and received ≥1 dose of investigational product) 1:1:1:1 Tezepelumab and matching PBO: Tezepelumab 70 mg SC Q4W (low dose; 138 patients), Tezepelumab 210 mg SC Q4W (medium dose; 137 patients), Tezepelumab 280 mg SC Q2W (high dose; 137 patients)
Comparator(s)	A placebo group (138 patients) who received placebo every 2 weeks for the duration of the trial

Trial name: PATHWAY	NCT number: NCT02054130
Follow-up time	52-weeks
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Primary Outcome Measures:** 1. Exposure adjusted incidence rates of AEs/SAEs (Baseline (Week 0 in predecessor study) to Week 104) Exposure adjusted rates defined as the number of events divided by person-time at risk **Secondary Outcome Measures:** 1. Annualized asthma exacerbation rate (AAER) (Baseline (Week 0 in predecessor study) to Week 104) The annualized exacerbation rate is based on exacerbations reported by the investigator in the eCRF
Method of analysis	Efficacy analyses conducted based on the ITT population Primary endpoint analysis conducted using negative binomial regression model with treatment group, baseline blood EOS and baseline ICS dose level as covariates Hierarchy was high-dose tezepelumab versus PBO Q4W + SoC, medium-dose tezepelumab versus PBO Q4W + SoC, and low-dose tezepelumab versus PBO Q4W + SoC There was >80% power to detect an AAER reduction of 40% at a two-side significance level of 10%
Subgroup analyses	• < and ≥150 cells/µL • 150 to <300 cells/µL • < and ≥300 cells/µL • 300 to <450 cells/µL • ≥450 cells/µL
Other relevant information	

Trial name: SOURCE	NCT number: NCT03406078
Objective	Study to Evaluate the Efficacy and Safety of Tezepelumab in Reducing Oral Corticosteroid Use in Adults with Oral Corticosteroid Dependent Asthma

Trial name: SOURCE	NCT number: NCT03406078
Publications – title, author, journal, year	Wechsler ME, Menzies-Gow A, Brightling CE, Kuna P, Korn S, Welte T, Griffiths JM, Sałapa K, Hellqvist Å, Almqvist G, Lal H, Kaur P, Skärby T, Colice G; SOURCE study group. Evaluation of the oral corticosteroid-sparing effect of tezepelumab in adults with oral corticosteroid-dependent asthma (SOURCE): a randomised, placebo-controlled, phase 3 study. Lancet Respir Med. 2022 Jul;10(7):650-660. doi: 10.1016/S2213-2600(21)00537-3. Epub 2022 Mar 29. Erratum in: Lancet Respir Med. 2022 Apr 5. Wechsler ME, Colice G, Griffiths JM, Almqvist G, Skärby T, Piechowiak T, Kaur P, Bowen K, Hellqvist Å, Mo M, Garcia Gil E. SOURCE: a phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy and safety of tezepelumab in reducing oral corticosteroid use in adults with oral corticosteroid dependent asthma. Respir Res. 2020 Oct 13;21(1):264. doi: 10.1186/s12931-020-01503-z.
Study type and design	A phase 3, multicenter, randomized, double-blind, placebo-controlled trial.
Sample size (n)	Patients (n=150) were randomized in a 1:1 ratio to receive tezepelumab 210 mg Q4W subcutaneously (administered using a single-use vial and syringe) or matching placebo Q4W for 48 weeks.

Main inclusion and exclusion criteria	**Inclusion criteria:** Subjects must have received a physician-prescribed medium- or high-dose ICS as per GINA guideline for at least 12 months Subjects must have received physician prescribed LABA and high dose ICS (total daily dose >500µg fluticasone propionate dry powder formulation equivalent) for at least 3 months. The ICS and LABA can be parts of a combination product or given by separate inhalers. Additional maintenance asthma controller medications are allowed according to standard practice of care i.e., leukotriene receptor antagonists (LTRAs), theophylline, long-acting muscarinic antagonists (LAMAs), secondary ICS and cromones. The use of these medications must be documented for at least 3 months Subjects must have received OCS for the treatment of asthma for at least 6 months prior to screening and on a stable dose of between ≥ 7.5 to ≤ 30mg (prednisone or prednisolone equivalent) daily or daily equivalent for at least 1 month. The OCS dose may be administered every other day (or different doses every other day); Average dose over two days = The daily dose. Morning pre-bronchodilator (BD) FEV1 must be < 80% predicted normal Subjects must have evidence of asthma as documented by post-BD (albuterol/salbutatomol) reversibility of FEV1 ≥12% and ≥200 mL (15-30 min after administration of 4 puffs of albuterol/salbutamol), documented either in the previous 12 months Subjects must have a history of at least 1 asthma exacerbation event within 12 months Minimum 10 days compliance with the morning and evening eDiary completion and OCS, ICS,LABA as well as other asthma controller medications as captured in the eDiary during the 14 days prior to randomization Documented physician-diagnosed asthma for at least 12 months **Exclusion criteria**: • Any clinically important pulmonary disease other than asthma (e.g. active lung infection, Chronic Obstructive Pulmonary Disease (COPD), bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency, and primary ciliary dyskinesia) or ever diagnosed with pulmonary or systemic disease, other than asthma, that are associated with elevated peripheral eosinophil counts (e.g. allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome). • Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, hematological, psychiatric, or major physical impairment that is not stable in the opinion of the Investigator and could: • Affect the safety of the subject throughout the study Influence the findings of the study or the interpretation Impede the subject's ability to complete the entire duration of study • History of cancer: Subjects who have had basal cell carcinoma, localized squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible to participate in the study provided that curative therapy was completed at least 12 months prior to visit 1.Subjects who have had other malignancies are eligible provided that curative therapy was completed at least 5 years • A helminth parasitic infection diagnosed within 6 months prior to screening that has not been treated with, or has failed to respond to, standard of care therapy. • Current smokers or subjects with smoking history ≥ 10 pack-years and subjects using vaping products, including electronic cigarettes. Former smokers with a smoking history of <10 pack years and users of vaping or e-cigarette products must have stopped for at least 6 months prior to visit 1 to be eligible. • History of chronic alcohol or drug abuse within 12 months • Tuberculosis requiring treatment within the 12 months

Trial name: SOURCE	NCT number: NCT03406078
	• History of any known immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test. • Major surgery within 8 weeks prior to visit 1 or planned surgical procedures requiring general anaesthesia or in-subject status for >1 day during the conduct of the study. • Clinically significant asthma exacerbation, in the opinion of the Investigator, including those requiring use of systemic corticosteroids or increase in the maintenance dose of OCS within 30 days
Intervention	Tezepelumab 210 mg Q4W subcutaneously (administered using a single-use vial and syringe).
Comparator(s)	Subcutaneously placebo Q4W
Follow-up time	60 weeks
Is the study used in the health economic model?	Yes

Primary, secondary and exploratory endpoints

Primary Outcome Measures:

1. Categorized Percent Reduction From Baseline in the Daily OCS Dose While Not Losing Asthma Control [Time Frame: Baseline to Week 48]
   Categorized percent reduction from baseline at Week 48. Percent change from baseline is defined as {final dose-baseline dose)/baseline dose} *100, and the categories of percent change from baseline in daily OCS dose are defined as: ≥90% to ≤100% reduction, ≥75% to <90% reduction, ≥50% to <75% reduction, >0% to <50% reduction, and, no change or any increase

Secondary Outcome Measures:

1. Annualised Asthma Exacerbation Rate (AAER) [Time Frame: Baseline to Week 48]
2. The annualized exacerbation rate is based on exacerbations reported by the investigator in the eCRF over 48 weeks.
3. Proportion of Subjects With 100% Reduction From Baseline in Daily OCS Dose at Week 48 [Time Frame: Baseline to Week 48]
4. Proportion (expressed as a percentage) of subjects with 100% reduction from baseline in daily OCS dose at Week 48. Percent change from baseline is defined as {(final dose-baseline dose)/baseline dose}*100.
5. Proportion of Subjects With Daily OCS Dose ≤5 mg at Week 48 [Time Frame: Week 48]
6. Proportion (expressed as a percentage) of subjects with daily OCS dose ≤5 mg at Week 48.
7. Proportion of Subjects With ≥50% Reduction From Baseline in Daily OCS Dose at Week 48 [Time Frame: Baseline to Week 48]
8. Proportion (expressed as a percentage) of subjects with ≥50% reduction from baseline in daily OCS dose at Week 48. Percent change from baseline is defined as {(final dose-baseline dose)/baseline dose}*100.
9. Change From Baseline in Pre-bronchodilator (Pre-BD) Forced Expiratory Volume in 1 Second (FEV1) [Time Frame: Baseline to Week 48]
10. Change from baseline in pre-BD FEV1 at Week 48. FEV1 is defined as the volume of air exhaled from the lungs in the first second of a forced expiration.
11. Change From Baseline in Weekly Mean Daily Asthma Symptom Score Via the Daily Asthma Symptom Diary [Time Frame: Baseline to Week 48]
12. Change from baseline in Asthma Symptom Diary score at Week 48. The Asthma Symptom Diary comprises of 10 items (5 items in the morning; 5 items in the evening). Asthma symptoms during night time and daytime are recorded by the patient each morning and evening in the daily diary. A daily ASD score is the mean of the 10 items. Responses for all 10 items are required to calculate the daily ASD score; otherwise, it is treated as missing. For the 7-day average asthma symptom score, scoring is done with no imputation using the mean of at least 4 of the 7 daily ASD scores as a mean weekly item score. The 7-day average ASD score ranges from 0 to 4, where 0 indicates no asthma symptoms.
13. Change From Baseline in Weekly Mean Rescue Medication Use [Time Frame: Baseline to Week 48]
14. Change from baseline in weekly mean rescue medication use at Week 48. Daily rescue medication use is defined as: Number of night inhaler puffs + 2 x [number of night nebulizer times] + number of daytime inhaler puffs + 2 x [number of day nebulizer times]. Each timepoint is calculated as weekly means based on daily diary data.
15. Change From Baseline in Weekly Mean Home Peak Expiratory Flow (PEF) (Morning and Evening) [Time Frame: Baseline to Week 48]
16. Change from baseline in weekly mean morning and evening peak expiratory flow (PEF) at Week 48. Home PEF testing will be performed by the subject in the morning upon

awakening and in the evening at bedtime using an electronic, hand-held spirometer. Each timepoint is calculated as weekly means using at least 4 of the 7 days of PEF data.

17. Change From Baseline in Weekly Mean Number of Night-time Awakening Due to Asthma [Time Frame: Baseline to Week 48]
18. Change from baseline in weekly mean number (expressed as a percentage) of night time awakenings at Week 48. Night-time awakenings percentage defined as number of nights with awakenings due to asthma and requiring rescue medication divided by number of nights with data and multiplied by 100%. At least 4 out of 7 days of data is required to calculate a weekly mean.
19. Change From Baseline in Asthma Control Questionnaire 6 (ACQ-6) Score [Time Frame: Baseline to Week 48]
20. Change from baseline in ACQ-6 at Week 48. The ACQ-6 captures asthma symptoms and short-acting β2-agonist use via subject-report. Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The ACQ-6 score is the mean of the responses.
21. Change From Baseline in Standardized Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ(s)+12) Total Score [Time Frame: Baseline to Week 48]
22. Change from baseline in AQLQ(S)+12 as compared to placebo at Week 48. The AQLQ(S)+12 is a questionnaire that measures the health-related quality of life experienced by asthma subjects. The total score is defined as the average of all 32 questions in the AQLQ(S)+12 questionnaire. AQLQ(S)+12 is a 7-point scale questionnaire, ranging from 7 (no impairment) to 1 (severe impairment).
23. Change From Baseline in European Quality of Life - 5 Dimensions 5 Levels Questionnaire (EQ-5D-5L) Score [Time Frame: Baseline to Week 48]
24. Change from baseline in EQ-5D-5L at Week 48. The EQ-5D-5L questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 response options (no/slight/moderate/severe/extreme problems) that reflect increasing levels of difficulty. The EQ-5D-5L scores are converted into a single index-based value (Health State Valuation), using the UK population-based weights. The Helth State Valuation is scored between 0 to 1, where higher score indicates a better health state.
25. Number of Participants With Asthma Specific Resource Utilizations [Time Frame: Baseline to Week 48]
26. Number of participants with asthma specific resource utilizations (e.g. unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications) over 48 weeks.
27. Change From Baseline in Work Productivity and Activity Impairment Questionnaire and Classroom Impairment Questionnaire (WPAI+CIQ) Score [Time Frame: Baseline to Week 48
28. Change from baseline in WPAI+CIQ score at Week 48. The WPAI+CIQ consists of 10 questions about how asthma and asthma related issues impact a subject's ability to work, attend classes, and perform regular daily activities.
29. Work (Class) productivity loss is derived by sum of percentage of missed work (class hours) due to asthma and product of percentage of actual working hours (class) times degree of asthma affecting work (class) productivity while working. Percentage of missed work (class hours) due to asthma is calculated by number of hours missed work (class) due to asthma divided by total number of hours missed work (class) plus number of hours actually worked (in class).
30. Activity impairment is the degree health affected regular activities (other than work or class) rated from 0 to 10, with 0 meaning no effect, divided by 10, and then expressed as a percentage.
31. Change From Baseline in FENO [Time Frame: Baseline to Week 48]

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32. Change from baseline in fractional exhaled nitric oxide (FeNO) at week 48.
33. Change From Baseline in Peripheral Blood Eosinophils [Time Frame: Baseline to Week 48]
34. Change from baseline in blood eosinophil counts at week 48.
35. Change From Baseline From Total Serum IgE [Time Frame: Baseline to Week 48]
36. Change from baseline in total serum IgE at week 48.
37. PK: Serum Trough Concentrations [Time Frame: Pre-dose samples at Baseline, Week 4, Week 12, Week 24, Week 40, Week 48, Week 60]
38. Serum trough concentrations at each scheduled visit.
39. Immunogenicity: Incidence of Anti-drug Antibodies (ADA) [Time Frame: Baseline to Week 60]
40. Anti-drug antibodies (ADA) responses at baseline and post baseline. Persistently positive is defined as positive at >=2 post baseline assessments (with >=16 weeks between the first and the last positive) or positive at last post baseline assessment. Transiently positive is defined as having at least one post baseline ADA positive assessment and not fulfilling the conditions of persistently positive. Treatment boosted ADA defined as baseline positive ADA that was boosted to a 4-fold or higher level following treatment. Treatment emergent ADA defined as sum of treatment induced ADA and treatment boosted ADA.

Method of analysis	• Two-sided hypotheses were evaluated in this trial at the 0.05 significance level. All other hypothesis testing in this study was considered exploratory

Subgroup analyses

- *Baseline eosinophils group: <300/µL, ≥300/µL*
- *Baseline eosinophils group: <150/µL, ≥150/µL*
- *Baseline eosinophils group: <150/µL, ≥ 150/µL to < 300/µL, ≥ 300/µL to <450/µL, ≥*
- *450/µL*
- *Baseline clinic visit FENO group: < 25ppb, ≥ 25ppb*
- *Baseline clinic visit FENO group: <25ppb, 25 to <50ppb, ≥50ppb*
- *Baseline (Any) specific IgE status (FEIA): Any FEIA positive, All FEIA negative,*
- *Unknown FEIA*
  - *"Any FEIA positive" requires 1 or more specific IgE panels using fluorescent enzyme immunoassay (FEIA) to be positive. Provided that at least one IgE panel is positive, no further requirement is made for data on all 12 panels to be available.*
  - *All FEIA negative" requires all 12 specific IgE panels to be negative. If there are fewer than 12 panels with data available and none of these is positive, then IgE status is considered "Unknown FEIA".*
  - *Positive is defined as a value ≥0.35 kU/L.*

** Baseline perennial specific IgE status (FEIA): Any perennial FEIA positive, All*

- *perennial FEIA negative, Unknown perennial FEIA*
  - *"Any perennial FEIA positive" requires 1 or more specific IgE (FEIA) panels to be positive. Provided that at least one IgE panel is positive, no further requirement is made for data on all 8 panels to be available.*
  - *"All perennial FEIA negative" requires all 8 specific IgE panels to be negative. If there are fewer than 8 panels with data available and none of these is positive, then IgE status is considered "Unknown perennial FEIA".*
  - *Positive is defined as a value ≥0.35 kU/L.*
  - *The 8 panels include: American Cockroach, Cat Dander, D. farina, D.pteronyssinus, Dog Dander, German Cockroach, Mould Mix, Oriental Cockroach.*
- *Baseline specific IgE status (FEIA): Any seasonal FEIA positive, All seasonal FEIA negative, Unknown seasonal FEIA*
  - *"Any seasonal FEIA positive" requires 1 or more specific IgE (FEIA) panels to be positive. Provided that at least one IgE panel is positive, no further requirement is made for data on all 4 panels to be available.*
  - *"All seasonal FEIA negative" requires all 4 specific IgE panels to be negative. If there are fewer than 4 panels with data available and none of these is positive, then IgE status is considered "Unknown seasonal FEIA".*
  - *Positive is defined as a value ≥0.35 kU/L.*
  - *The 4 panels include: Grass Mix Pollen, Silver Birch Pollen, Weed Mix Pollen, Japanese Cedar.*
- *Daily OCS dose at baseline: (≤10 mg versus >10 mg prednisone or prednisolone)*
- *Age category: age (≥18 to <65) and age (≥65)*
- *Gender: Male/Female*
- *Race: White, Black or African American, Asian, Native Hawaiian or Other Pacific*
- *Islander, American Indian or Alaska Native, Other*
- *Baseline body mass index (BMI): <18.5 kg/m2 18.5 to <25.0 kg/m2, 25.0 to <30.0 kg/m2 ≥30.0 kg/m2*

Trial name: SOURCE	NCT number: NCT03406078
	• *Baseline body mass index (BMI): <30 kg/m2≥30 kg/m2* • *Geographical region: Western Europe and North America (incl. Germany and USA); Central/Eastern Europe (incl. Poland, Turkey and Ukraine); Rest of World (incl. Argentina* • *and South Korea).* • *Country*

Trial name: Wentzel et al. Lancet 2016; 388: 31–44	NCT number: NCT01854047
Objective	To evaluate the efficacy of different doses and regimens of dupilumab in participants with moderate to severe uncontrolled asthma.
Publications – title, author, journal, year	Wenzel Sally et al.: Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. Lancet 2016 Jul 2;388(10039):31-44. doi: 10.1016/S0140-6736(16)30307-5. Epub 2016 Apr 27.
Study type and design	A randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial.. First patient: June 2013. Last patient: November 2015
Sample size (n)	Patients (n=769) were randomized in a 1:1:1:1 ratio to receive subcutaneous dupilumab 200 mg or 300 mg every 2 weeks or every 4 weeks, or placebo, over a 24-week period

Trial name: Wentzel et al. Lancet 2016; 388: 31–44	NCT number: NCT01854047

Main inclusion and exclusion criteria

Inclusion criteria:

Participants with a physician diagnosis of moderate to severe, uncontrolled asthma for >=12 months, based on the Global Initiative for Asthma (GINA) 2009 Guidelines and:

- Existing treatment with moderate or high-dose inhaled corticosteroid / long-acting beta-2 agonist
- Forced expiratory volume (FEV1) 40 to 80% of predicted normal
- Asthma Control Questionnaire, 5-question version (ACQ-5) score >=1.5
- Reversibility of at least 12% and 200 mL in forced expiratory volume (FEV1)
- Had experienced, within prior year: hospitalization, emergency or urgent care visit or systemic corticosteroid treatment for worsening asthma

Exclusion criteria:

Participants <18 years

Chronic obstructive pulmonary disease (COPD) or other lung diseases (eg, emphysema, idiopathic pulmonary fibrosis, Churg-Strauss syndrome, allergic bronchopulmonary aspergillosis) which impaired pulmonary function tests

Chest X-ray within 12 months of screening visit or at screening visit with clinically significant findings of lung disease(s) other than asthma

Current smoker or cessation of smoking within 6 months prior to Visit 1

Previous smoker with a smoking history >10 pack-years

Trial name: Wentzel et al. Lancet 2016; 388: 31–44		NCT number: NCT01854047
Intervention	Patients received masked subcutaneous administrations of dupilumab or matching placebo every 2 weeks or every 4 weeks on their first day of treatment until week 24 as follows: dupilumab 200 mg (every 2 weeks and every 4 weeks), loading dose of 400 mg; dupilumab 300 mg (every 2 weeks and every 4 weeks), loading dose of 600 mg; or placebo; followed by a 16-week post-treatment follow-up period to monitor patients after treatment. Patients continued background therapy with inhaled corticosteroids plus a long-acting β2-agonist at a stable dose throughout the randomised treatment period and during follow-up. Throughout the study, and as needed, patients were allowed to administer a short-acting β 2-adrenergic receptor agonist (either salbutamol or levosalbutamol) as relief medication for asthma symptoms. Concomitant medications were permitted during the study; exceptions are listed in the appendix. Study assessments were done every 2 weeks from baseline to week 12, followed by every 4 weeks until week 24, and every 4 weeks during the 16-week follow-up period	
Comparator(s)	Subcutaneously placebo QW2 or QW4	
Follow-up time	24 weeks followed by a 16-week post-treatment follow-up period	
Is the study used in the health economic model?	Yes	

Primary, secondary and exploratory endpoints

1. Percent Change From Baseline in FEV1 at Week 12: HEos-ITT Population [Time Frame: Baseline, Week 12]FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer.
2. Percent Change From Baseline in FEV1 at Week 12: ITT Population [Time Frame: Baseline, Week 12] FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer.
3. Annualized Event Rate of Severe Exacerbation During The Treatment Period: HEos-ITT Population Time Frame: Baseline to Week 24] A severe exacerbation was defined as a deterioration of asthma requiring: use of systemic corticosteroids for >=3 days; or hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids. Annualized event rate was the total number of exacerbations that occurred during the treatment period divided by the total number of participant-years treated.
4. Annualized Event Rate of Severe Exacerbation During The Treatment Period: ITT Population [Time Frame: Baseline to Week 24] A severe exacerbation was defined as a deterioration of asthma requiring: use of systemic corticosteroids for >=3 days; or hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids. Annualized event rate was the total number of exacerbations that occurred during the treatment period divided by the total number of participant-years treated.
5. Time to First Severe Exacerbation: Kaplan-Meier Estimates at Week 12 and 24: HEos-ITT Population [Time Frame: Baseline up to Week 24] The time to first severe exacerbation was defined as the time from the date of first dose to the date of the first severe exacerbation event. For participants who had no severe exacerbation on or before last dose date + 14 days, it was censored at the date of last dose date + 14 days. The median time to first severe exacerbation was not estimated because the number of severe exacerbations was too low in the Dupilumab arms. Therefore, alternative Kaplan-Meier statistics, the probability of severe exacerbation at Week 12 and 24, are presented as the descriptive measure statistics.
6. Time to First Severe Exacerbation: Kaplan-Meier Estimates at Week 12 and 24: ITT Population [Time Frame: Baseline up to Week 24] The time to first severe exacerbation was defined as the time from the date of first dose to the date of the first severe exacerbation event. For participants who had no severe exacerbation on or before last dose date + 14 days, it was censored at the date of last dose date + 14 days. The median time to first severe exacerbation was not estimated because the number of severe exacerbations was too low in the Dupilumab arms. Therefore, alternative Kaplan-Meier statistics, the probability of severe exacerbation at Week 12 and 24, are presented as the descriptive measure statistics.
7. Annualized Event Rate of Loss of Asthma Control (LOAC) During The Treatment Period: HEos-ITT Population [Time Frame: Baseline to Week 24] LOAC was defined as any of the following: >=6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24-hour period (compared to baseline) on 2 consecutive days; increase in inhaled corticosteroid (ICS) >=4 times the dose at randomization; use of systemic corticosteroids for >=3 days; hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids. Annualized event rate was the total number of LOAC that occurred during the treatment period divided by the total number of participant-years treated.
8. Annualized Event Rate of LOAC During The Treatment Period: ITT Population [Time Frame: Baseline to Week 24] LOAC was defined as any of the following: >=6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24-hour period (compared to baseline) on 2 consecutive days; increase in ICS >=4 times the dose at randomization; use of systemic corticosteroids for >=3 days; hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids. Annualized event rate was the total number of LOAC that occurred during the treatment period divided by the total number of participant-years treated.
9. Time to First LOAC Event: Kaplan-Meier Estimates at Week 12 and Week 24: HEos-ITT Population [Time Frame: Baseline up to Week 24] The time to first LOAC event was defined

as the time from the date of first dose to the date of the first LOAC event. For participants who had no LOAC event on or before last dose date + 14 days, it was censored at the date of last dose date + 14 days. The median time to first LOAC was not estimated because the number of LOAC was too low in the Dupilumab arms. Therefore, alternative Kaplan-Meier statistics, the probability of LOAC at Week 12 and 24, are presented as the descriptive measure statistics.

10. Time to First LOAC Event: Kaplan-Meier Estimates at Week 12 and Week 24: ITT Population [Time Frame: Baseline up to Week 24] The time to first LOAC event was defined as the time from the date of first dose to the date of the first LOAC event. For participants who had no LOAC event on or before last dose date + 14 days, it was censored at the date of last dose date + 14 days. The median time to first LOAC was not estimated because the number of LOAC was too low in the Dupilumab arms. Therefore, alternative Kaplan-Meier statistics, the probability of LOAC at Week 12 and 24, are presented as the descriptive measure statistics.
11. Change From Baseline in Morning Asthma Symptom Score at Week 12: HEos-ITT Population [Time Frame: Baseline, Week 12] Morning asthma symptom score was determined using AM (ante meridiem) symptom scoring system which evaluated participant's overall asthma symptoms experienced during the night. It ranged from 0 to 4 as: 0 = No asthma symptoms, slept through the night, 1= Slept well, but some complaints in the morning, no night-time awakenings, 2= Woke up once because of asthma (including early awakening), 3= Woke up several times because of asthma (including early awakening), 4= Bad night, awake most of the night because of asthma.
12. Change From Baseline in Morning Asthma Symptom Score at Week 12: ITT Population [Time Frame: Baseline, Week 12] Morning asthma symptom score was determined using AM symptom scoring system which evaluated participant's overall asthma symptoms experienced during the night. It ranged from 0 to 4 as: 0 = No asthma symptoms, slept through the night, 1= Slept well, but some complaints in the morning, no night-time awakenings, 2= Woke up once because of asthma (including early awakening), 3= Woke up several times because of asthma (including early awakening), 4= Bad night, awake most of the night because of asthma.
13. Change From Baseline in Evening Asthma Symptom Score at Week 12: HEos-ITT Population [Time Frame: Baseline, Week 12] Evening asthma symptom score was determined using PM (post meridiem) symptom scoring system which evaluated participant's overall asthma symptoms experienced during the day. It ranged from 0 to 4 as: 0=very well, no asthma symptoms, 1=one episode of wheezing, cough, or breathlessness, 2=more than one episode of wheezing, cough, or breathlessness without interference of normal activities, 3=wheezing, cough, or breathlessness most of the day, which interfered to some extent with normal activities, 4=asthma very bad, unable to carry out daily activities as usual.
14. Change From Baseline in Evening Asthma Symptom Score at Week 12: ITT Population [Time Frame: Baseline, Week 12] Evening asthma symptom score was determined using PM symptom scoring system which evaluated participant's overall asthma symptoms experienced during the day. It ranged from 0 to 4 as: 0=very well, no asthma symptoms, 1=one episode of wheezing, cough, or breathlessness, 2=more than one episode of wheezing, cough, or breathlessness without interference of normal activities, 3=wheezing, cough, or breathlessness most of the day, which interfered to some extent with normal activities, 4=asthma very bad, unable to carry out daily activities as usual.
15. Change From Baseline in Asthma Control Questionnaire 5-item Version (ACQ-5) Score at Week 12: HEos-ITT Population [Time Frame: Baseline, Week 12] The ACQ-5 has 5 questions, reflecting the top-scoring five asthma symptoms: woken at night by symptoms, wake in the mornings with symptoms, limitation of daily activities, shortness of breath and wheeze. Participants were asked to recall how their asthma had been during the previous week and to respond to each of the five symptom questions on a 7-point scale ranged from 0 (no impairment) to 6 (maximum impairment). ACQ-5 total score was mean of the scores of all 5 questions and, therefore, ranged from 0 (totally controlled) to 6 (severely uncontrolled). Higher score indicated lower asthma control.

16. Change From Baseline in ACQ-5 Score at Week 12: ITT Population [Time Frame: Baseline, Week 12] The ACQ-5 has 5 questions, reflecting the top-scoring five asthma symptoms: woken at night by symptoms, wake in the mornings with symptoms, limitation of daily activities, shortness of breath and wheeze. Participants were asked to recall how their asthma had been during the previous week and to respond to each of the five symptom questions on a 7-point scale ranged from 0 (no impairment) to 6 (maximum impairment). ACQ-5 total score was mean of the scores of all 5 questions and, therefore, ranged from 0 (totally controlled) to 6 (severely uncontrolled). Higher score indicated lower asthma control.
17. Change From Baseline in Asthma Quality of Life Questionnaire (AQLQ) Global Score at Week 12: HEos-ITT Population [Time Frame: Baseline, Week 12] The AQLQ is a disease-specific, self-administered quality of life questionnaire designed to measure functional impairments that are most important to participants with asthma. The AQLQ comprises of 32 items in 4 domains: symptoms (12 items), activity limitation (11 items), emotional function (5 items), environmental stimuli (4 items). Each item is scored on a 7-point Likert scale (1=maximal impairment, 7=no impairment). The 32 items of the questionnaire are averaged to produce one overall quality of life score ranging from 1 (severely impaired) to 7 (not impaired at all). Higher scores indicate better quality of life.
18. Change From Baseline in AQLQ Global Score at Week 12: ITT Population [Time Frame: Baseline, Week 12] The AQLQ is a disease-specific, self-administered quality of life questionnaire designed to measure functional impairments that are most important to participants with asthma. The AQLQ comprises of 32 items in 4 domains: symptoms (12 items), activity limitation (11 items), emotional function (5 items), environmental stimuli (4 items). Each item is scored on a 7-point Likert scale (1=maximal impairment, 7=no impairment). The 32 items of the questionnaire are averaged to produce one overall quality of life score ranging from 1 (severely impaired) to 7 (not impaired at all). Higher scores indicate better quality of life.
19. Change From Baseline in Number of Inhalations Per Day of Salbutamol/Albuterol or Levosalbutamol/Levalbuterol at Week 12: HEos-ITT Population [Time Frame: Baseline, Week 12]Participants might administered salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication as needed during the study. The number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations were recorded by the participants in their electronic diary.
20. Change From Baseline in Number of Inhalations Per Day of Salbutamol/Albuterol or Levosalbutamol/Levalbuterol at Week 12: ITT Population [Time Frame: Baseline, Week 12] Participants might administered salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication as needed during the study. The number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations were recorded by the participants in their electronic diary.

Trial name: Wentzel et al. Lancet 2016; 388: 31–44	NCT number: NCT01854047
Method of analysis	• The primary efficacy endpoint and continuous secondary endpoint variables were analysed with a mixed-effects model with a repeated-measures model with a repeated-measures approach • The annualised rate of severe asthma exacerbation events during the treatment period only was analysed with a negative binomial regression model, including the total number of events occurring during the double-blind treatment period as the response variable; treatment group, baseline blood eosinophil strata, pooled countries or regions, and number of asthma events in the year before the study as covariates; and log-transformed treatment duration as the offset variable • Time to severe exacerbation was analysed using a Cox regression model with time to exacerbation event as the dependent variable and treatment group, baseline blood eosinophil strata, number of asthma events in the year before the study, and pooled countries or regions as covariates. • The Kaplan-Meier method was used to derive the proportion of patients with an event at weeks 12 and 24 specific to each treatment group. • Safety variables, including adverse events, laboratory variables, vital signs, electrocardiograms, and physical examinations, were summarised with descriptive statistics. • For the primary endpoint, enrolment of 60 patients per group with eosinophil counts of at least 300 eosinophils per µL provided 83% power to detect a difference in FEV1 change of 0·2 L between the highest dupilumab dose and placebo, assuming the common SD was 0·35, with a two-sided test at a 0·05 significance level and an expected dropout rate of 10% by week 12.

Trial name: LIBERTY ASTHMA QUEST Busse et al. Adv Ther (2018) 35:737–748	NCT number: NCT02414854
Objective	To evaluate the efficacy of dupilumab (SAR231893 / REGN668) in participants with persistent asthma.
Publications – title, author, journal, year	Busse WW et al: Liberty Asthma QUEST: Phase 3 Randomized, Double-blind, Placebo-Controlled, Parallel-Group Study to Evaluate Dupilumab Efficacy/Safety in Patients with Uncontrolled, Moderate-to-Severe Asthma. Adv Ther (2018) 35:737–748 https://doi.org/10.1007/s12325-018-0702-4
Study type and design	Phase 3 Randomized, Double-blind, Placebo-Controlled, Parallel-Group Study
Sample size (n)	A total of 1902 patients (aged ≥ 12 years)

Trial name: LIBERTY ASTHMA QUEST Busse et al. Adv Ther (2018) 35:737–748	NCT number: NCT02414854
Main inclusion and exclusion criteria	**Inclusion criteria:** Adults and adolescent participants with a physician diagnosis of asthma for ≥12 months, based on the Global Initiative for Asthma (GINA) 2014 Guidelines and the following criteria: Existing treatment with medium to high dose ICS (≥250 mcg of fluticasone propionate twice daily or equipotent ICS daily dosage to a maximum of 2000 mcg/day of fluticasone propionate or equivalent) in combination with a second controller (eg, long-acting beta agonist, leukotriene receptor antagonist) for at least 3 months with a stable dose ≥1 month prior to Visit 1. Note for Japan: for participants aged 18 years and older, ICS must be on ≥200 mcg of fluticasone propionate twice daily or equivalent; for participants aged 12 to 17 years, ICS must be ≥100 mcg of fluticasone propionate twice daily or equivalent). Participants requiring a third controller for their asthma will be considered eligible for this study, and it should also be used for at least 3 months with a stable dose ≥1 month prior to Visit 1. **Exclusion criteria:** • Participants <12 years of age or the minimum legal age for adolescents in the country of the investigative site, whichever is higher (For those countries where local regulations permit enrolment of adults only, participant recruitment will be restricted to those who are ≥18 years of age). • Weight is less than 30 kilograms. • Chronic obstructive pulmonary disease or other lung diseases (eg, idiopathic pulmonary fibrosis, Churg-Strauss Syndrome, etc) which may impair lung function. • A participant who experiences a severe asthma exacerbation (defined as a deterioration of asthma that results in emergency treatment, hospitalization due to asthma, or treatment with systemic steroids at any time from 1 month prior to the Screening Visit up to and including the Baseline Visit). • Evidence of lung disease(s) other than asthma, either clinical evidence or imaging (Chest X-ray, CT, MRI) within 12 months of Visit 1 or at the screening visit, as per local standard of care. • Note for Japan: According to the request from the health authority, chest X-ray should be performed at screening visit if there is no chest imaging (Chest X-ray, computed tomography [CT], magnetic resonance imaging [MRI]) available within 3 months prior to screening to exclude participants with suspected active or untreated latent tuberculosis. • Current smoker or cessation of smoking within 6 months prior to Visit 1. • Previous smoker with a smoking history >10 pack-years. • Comorbid disease that might interfere with the evaluation of Investigational Medicinal Product.
Intervention	Subjects were randomized in a 2:2:1:1 ratio to receive 52 weeks of add-on therapy with subcutaneously administered dupilumab 200 or 300 mg every 2 weeks or matched placebo
Comparator(s)	Dupilumab 200 or 300 mg or matched placebo
Follow-up time	52-week randomized treatment period, and 12-week post-treatment follow-up period
Is the study used in the health economic model?	Yes

Primary, secondary and exploratory endpoints

1. Annualized Rate of Severe Exacerbation Events During The 52-Week Treatment Period: Intent-to-Treat (ITT) Population [Time Frame: Baseline to Week 52] A severe exacerbation was defined as a deterioration of asthma requiring: use of systemic corticosteroids for >=3 days; or hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids. Annualized event rate was the total number of exacerbations that occurred during the treatment period divided by the total number of participant-years treated.
2. Absolute Change From Baseline in Pre-Bronchodilator Forced Expiratory Volume in 1 Second (FEV1) at Week 12: ITT Population [Time Frame: Baseline, Week 12] FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer.
3. Percent Change From Baseline in Pre-Bronchodilator FEV1 at Week 12: ITT Population [Time Frame: Baseline, Week 12] FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer.
4. Annualized Rate of Severe Exacerbation Events During The 52-Week Treatment Period: ITT Population With Baseline Eosinophil >=0.15 Giga/L [Time Frame: Baseline to Week 52]A severe exacerbation was defined as a deterioration of asthma requiring: use of systemic corticosteroids for >=3 days; or hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids. Annualized event rate was the total number of exacerbations that occurred during the treatment period divided by the total number of participant-years treated.
5. Absolute Change From Baseline in Pre-Bronchodilator FEV1 at Week 12: ITT Population With Baseline Eosinophil >=0.15 Giga/L [Time Frame: Baseline, Week 12]FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer.
6. Annualized Rate of Severe Exacerbation Events During The 52-Week Treatment Period: ITT Population With Baseline Eosinophil >=0.3 Giga/L [Time Frame: Baseline to Week 52]A severe exacerbation was defined as a deterioration of asthma requiring: use of systemic corticosteroids for >=3 days; or hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids. Annualized event rate was the total number of exacerbations that occurred during the treatment period divided by the total number of participant-years treated.
7. Absolute Change From Baseline in Pre-Bronchodilator FEV1 at Week 12: ITT Population With Baseline Eosinophil >=0.3 Giga/L [Time Frame: Baseline, Week 12]FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer.
8. Annualized Rate of Severe Exacerbation Events During The 52-Week Treatment Period: ITT Population With Baseline Eosinophil <0.3 Giga/L [Time Frame: Baseline to Week 52]A severe exacerbation was defined as a deterioration of asthma requiring: use of systemic corticosteroids for >=3 days; or hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids. Annualized event rate was the total number of exacerbations that occurred during the treatment period divided by the total number of participant-years treated.
9. Annualized Rate of Severe Exacerbation Events During The 52-Week Treatment Period: ITT Population With High Dose ICS at Baseline [Time Frame: Baseline to Week 52]A severe exacerbation was defined as a deterioration of asthma requiring: use of systemic corticosteroids for >=3 days; or hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids. Annualized event rate was the total number of exacerbations that occurred during the treatment period divided by the total number of participant-years treated.
10. Absolute Change From Baseline in Pre-Bronchodilator FEV1 at Week 12: ITT Population With High Dose ICS at Baseline [Time Frame: Baseline, Week 12]FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer.

11. Change From Baseline in Asthma Quality of Life Questionnaire With Standardized Activities (AQLQ [S]) Self-Administered Global Score at Week 24: ITT Population [Time Frame: Baseline, Week 24]The AQLQ is a disease-specific, self-administered quality of life questionnaire designed to measure functional impairments that are most important to participants with asthma. The AQLQ comprises of 32 items in 4 domains: symptoms (12 items), activity limitation (11 items), emotional function (5 items), environmental stimuli (4 items). Each item is scored on a 7-point likert scale (1=maximal impairment, 7=no impairment). The 32 items of the questionnaire are averaged to produce one overall quality of life score ranging from 1 (severely impaired) to 7 (not impaired at all). Higher scores indicate better quality of life.
12. Change From Baseline in AQLQ (S) Self- Administered Global Score at Week 24: ITT Population With Baseline Eosinophil >=0.3 Giga/L [Time Frame: Baseline, Week 24]The AQLQ is a disease-specific, self-administered quality of life questionnaire designed to measure functional impairments that are most important to participants with asthma. The AQLQ comprises of 32 items in 4 domains: symptoms (12 items), activity limitation (11 items), emotional function (5 items), environmental stimuli (4 items). Each item is scored on a 7-point likert scale (1=maximal impairment, 7=no impairment). The 32 items of the questionnaire are averaged to produce one overall quality of life score ranging from 1 (severely impaired) to 7 (not impaired at all). Higher scores indicate better quality of life.
13. Change From Baseline in Asthma Control Questionnaire 5-item Version (ACQ-5) Score at Week 24: ITT Population [Time Frame: Baseline, Week 24]The ACQ-5 has 5 questions, reflecting the top-scoring five asthma symptoms: woken at night by symptoms, wake in the mornings with symptoms, limitation of daily activities, shortness of breath and wheeze. Participants were asked to recall how their asthma had been during the previous week and to respond to each of the five symptom questions on a 7-point scale ranged from 0 (no impairment) to 6 (maximum impairment). ACQ-5 total score was mean of the scores of all 5 questions and, therefore, ranged from 0 (totally controlled) to 6 (severely uncontrolled). Higher score indicated lower asthma control.
14. Annualized Rate of Severe Exacerbation Events Resulting in Hospitalization or Emergency Room Visit During The 52-Week Treatment Period: ITT Population [Time Frame: Baseline to Week 52]A severe exacerbation was defined as a deterioration of asthma requiring: use of systemic corticosteroids for >=3 days; or hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids. Annualized event rate was the total number of exacerbations (resulted hospitalization or emergency room visit) that occurred during the treatment period divided by the total number of participant-years treated.
15. Absolute Change From Baseline in Pre-Bronchodilator FEV1 at Week 12: ITT Population With Baseline Eosinophil <0.3 Giga/L [Time Frame: Baseline, Week 12]FEV1 was the volume of air exhaled in the first second of a forced expiration a measured by spirometer.
16. Percent Change From Baseline in Pre-Bronchodilator FEV1 at Week 12: ITT Population With Baseline Eosinophil >=0.3 Giga/L [Time Frame: Baseline, Week 12]FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer.
17. Percent Change From Baseline in Pre-Bronchodilator FEV1 at Week 12: ITT Population With High Dose ICS at Baseline [Time Frame: Baseline, Week 12]FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer.
18. Percent Change From Baseline in Pre-Bronchodilator FEV1 at Week 12: ITT Population With Baseline Eosinophil >=0.15 Giga/L [Time Frame: Baseline, Week 12]FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer.

19. Absolute Change From Baseline in Pre-Bronchodilator FEV1 at Weeks 2, 4, 8, 24, 36, and 52: ITT Population [Time Frame: Baseline, Weeks 2, 4, 8, 24, 36, and 52]FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer.
20. Percent Change From Baseline in Pre-Bronchodilator FEV1 at Weeks 2, 4, 8, 24, 36, and 52: ITT Population [Time Frame: Baseline, Weeks 2, 4, 8, 24, 36, and 52]FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer.
21. Change From Baseline in Percent Predicted FEV1 at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population [Time Frame: Baseline, Weeks 2, 4, 8, 12, 24, 36, and 52]FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer.
22. Change From Baseline in Morning (AM)/Evening (PM) Peak Expiratory Flow (PEF) at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population [Time Frame: Baseline, Weeks 2, 4, 8, 12, 24, 36, and 52]The PEF is a participant's maximum speed of expiration, as measured with a peak flow meter. Peak flow testing for PEF was performed at home (morning and evening) while sitting or standing prior to using any medication (if needed) for asthma.
23. Change From Baseline in Forced Vital Capacity (FVC) at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population [Time Frame: Baseline, Weeks 2, 4, 8, 12, 24, 36, and 52]FVC is a standard pulmonary function test used to quantify respiratory muscle weakness. FVC is the volume of air that can forcibly be blown out after full inspiration in the upright position, measured in liters.
24. Change From Baseline in Forced Expiratory Flow (FEF) 25-75% at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population [Time Frame: Baseline, Weeks 2, 4, 8, 12, 24, 36, and 52]FEF is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation. FEF25-75% is defined as the mean forced expiratory flow between the 25% and 75% of the FVC.
25. Change From Baseline in Post-Bronchodilator FEV1 at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population [Time Frame: Baseline, Weeks 2, 4, 8, 12, 24, 36, and 52]FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer.
26. Annualized Rate of Loss of Asthma Control (LOAC) Event During The 52-Week Treatment Period: ITT Population [Time Frame: Baseline to Week 52]LOAC was defined as any of the following: >=6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24-hour period (compared to baseline) on 2 consecutive days; increase in ICS >=4 times the dose at randomization; use of systemic corticosteroids for >=3 days; hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids. Annualized event rate was the total number of LOAC that occurred during the treatment period divided by the total number of participant-years treated.
27. Time to First Severe Exacerbation Event: Kaplan-Meier Estimates During The 52-Week Treatment Period: ITT Population [Time Frame: Baseline up to Week 52]The time to first severe exacerbation was defined as follows: date of the first event - randomization date +1. For participants who had no event on or before Visit 18 (Week 52) or last contact date, the time was censored at the date of Visit 18 or the last contact date, whichever was earlier. The median time to first severe exacerbation was not estimated; therefore, the probability of severe exacerbation at Weeks 12, 24, 36, and 52, are presented as the descriptive statistics.
28. Time to First LOAC Event: Kaplan-Meier Estimates During The 52-Week Treatment Period: ITT Population [Time Frame: Baseline up to Week 52]The time to first LOAC event was defined as follows: date of the first event - first dose date +1. For participants who had no event on or before last dose date + 14 days or last contact

date, the time was censored at the last dose date + 14 days or the last contact date, whichever was earlier.

29. Change From Baseline in ACQ-5 Score at Weeks 2, 4, 8, 12, 36, and 52: ITT Population [Time Frame: Baseline, Weeks 2, 4, 8, 12, 36, and 52]The ACQ-5 has 5 questions, reflecting the top-scoring five asthma symptoms: woken at night by symptoms, wake in the mornings with symptoms, limitation of daily activities, shortness of breath and wheeze. Participants were asked to recall how their asthma had been during the previous week and to respond to each of the five symptom questions on a 7-point scale ranged from 0 (no impairment) to 6 (maximum impairment). ACQ-5 total score was mean of the scores of all 5 questions and, therefore, ranged from 0 (totally controlled) to 6 (severely uncontrolled). Higher score indicated lower asthma control.
30. Change From Baseline in Asthma Control Questionnaire 7-item Version (ACQ-7) Score at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population [Time Frame: Baseline, Weeks 2, 4, 8, 12, 24, 36, and 52]The ACQ-7 has 7 questions, the first 5 questions assess the most common asthma symptoms: woken at night by symptoms, wake in the mornings with symptoms, limitation of daily activities, shortness of breath and wheeze plus short-acting bronchodilator use, and FEV1 (pre-bronchodilator % predicted). Participants were asked to recall how their asthma had been during the previous week and to respond to each of the five symptom questions on a 7-point scale ranged from 0 (no impairment) to 6 (maximum impairment). Clinic staff scored the FEV1% predicted on a 7-point scale. The questions were equally weighted and the ACQ-7 total score was mean of the scores of all 7 questions and, therefore, ranged from 0 (totally controlled) to 6 (severely uncontrolled). Higher score indicated lower asthma control.
31. Change From Baseline in Morning Asthma Symptom Score at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population [Time Frame: Baseline, Weeks 2, 4, 8, 12, 24, 36, and 52]Morning asthma symptom score was determined using AM (ante meridiem) symptom scoring system which evaluated participant's overall asthma symptoms experienced during the night. It ranged from 0 to 4 as: 0= No asthma symptoms, slept through the night, 1= Slept well, but some complaints in the morning, no night time awakenings, 2= Woke up once because of asthma (including early awakening), 3= Woke up several times because of asthma (including early awakening), 4= Bad night, awake most of the night because of asthma.
32. Change From Baseline in Evening Asthma Symptom Score at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population [Time Frame: Baseline, Weeks 2, 4, 8, 12, 24, 36, and 52]Evening asthma symptom score was determined using PM (post meridiem) symptom scoring system which evaluated participant's overall asthma symptoms experienced during the day. It ranged from 0 to 4 as: 0=very well, no asthma symptoms, 1=one episode of wheezing, cough, or breathlessness, 2=more than one episode of wheezing, cough, or breathlessness without interference of normal activities, 3=wheezing, cough, or breathlessness most of the day, which interfered to some extent with normal activities, 4=asthma very bad, unable to carry out daily activities as usual.
33. Change From Baseline in Number of Nocturnal Awakenings Per Night at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population [Time Frame: Baseline, Weeks 2, 4, 8, 12, 24, 36, and 52]Participants recorded every morning on awakening the number of asthma-related nocturnal awakenings requiring use of rescue medication that occurred during the previous night.
34. Change From Baseline in Number of Puffs of Daily Reliever Medication Used Per 24 Hours at Weeks 2, 4, 8, 12, 24, 36, and 52: ITT Population [Time Frame: Baseline, Weeks 2, 4, 8, 12, 24, 36, and 52]Participants might administered salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication as needed during the study. The number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations were recorded daily by the participants in an electronic diary/peak expiratory flow (PEF) meter. In the case that Nebulizer solutions

were used as an alternative delivery method, the nebulizer dose was converted to number of puffs as per following conversion factor: salbutamol/albuterol nebulizer solution (2.5 mg) corresponds to 4 puffs.

35. Change From Baseline in AQLQ (S) Self-Administered Global Score at Weeks 12, 36, and 52: ITT Population [Time Frame: Baseline, Weeks 12, 36, and 52]The AQLQ is a disease-specific, self-administered quality of life questionnaire designed to measure functional impairments that are most important to participants with asthma. The AQLQ comprises of 32 items in 4 domains: symptoms (12 items), activity limitation (11 items), emotional function (5 items), environmental stimuli (4 items). Each item is scored on a 7-point likert scale (1=maximal impairment, 7=no impairment). The 32 items of the questionnaire are averaged to produce one overall quality of life score ranging from 1 (severely impaired) to 7 (not impaired at all). Higher scores indicate better quality of life.
36. Change From Baseline in European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L) Scores at Weeks 12, 24, 36, and 52: ITT Population [Time Frame: Baseline, Weeks 12, 24, 36, and 52]EQ-5D-5L is a standardized health-related quality of life questionnaire developed by EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. EQ-5D consists of EQ-5D descriptive system and EQ visual analogue scale (VAS). EQ-5D descriptive system comprises of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The 5D-5L systems are converted into a single index utility score between 0 to 1, where higher score indicates a better health state. EQ-5D-5L-VAS records participant's self-rated health on a vertical VAS that allows them to indicate their health state that can range from 0 (worst imaginable) to 100 (best imaginable).
37. Change From Baseline in Hospital Anxiety and Depression Scale (HADS) Total Score at Weeks 12, 24, 36, and 52: ITT Population [Time Frame: Baseline, Weeks 12, 24, 36, and 52]The HADS is a general scale to detect states of anxiety and depression already used and validated in asthma, which includes HADS-A and HADS-D subscales. The instrument is comprised of 14 items: 7 related to anxiety (HADS-A) and 7 to depression (HADS-D). Each item on the questionnaire is scored from 0-3. The anxiety/depression score is the sum of the scores of the 7 related items; one can score between 0 and 21 for either anxiety or depression. And the total score is the sum of the scores of the 14 items ranging from 0 (no symptoms) to 42 (severe symptoms), with higher scores indicating higher anxiety/depression complains.
38. Change From Baseline in 22-Item Sino Nasal Outcome Test (SNOT-22) Score at Weeks 12, 24, 36, and 52: ITT Population With Bilateral Nasal Polyposis/Chronic Rhinosinusitis [Time Frame: Baseline, Weeks 12, 24, 36, and 52]The SNOT-22 is a validated measure of health related quality of life in sinonasal disease. It is a 22 item questionnaire with each item assigned a score ranging from 0-5. The total score may range from 0 (no disease) -110 (worst disease), lower scores represent better health related quality of life.
39. Change From Baseline in Standardized Rhinoconjunctivitis Quality Of Life Questionnaire, Ages 12+ (RQLQ[S]+12) Score at Weeks 12, 24, 36, and 52: ITT Population With Comorbid Allergic Rhinitis [Time Frame: Baseline, Weeks 12, 24, 36, and 52]RQLQ(S)+12 is a self-administered questionnaire with standardized activities developed to measure health-related quality of life signs and symptoms that are most problematic in those 12 to 75 years of age, as a result of perennial or seasonal allergic rhinitis. There are 28 items on RQLQ(S) in 7 domains: activities (3 items), sleep (3 items), non-nose/eye symptoms (7 items), practical problems (3 items), nasal symptoms (4 items), eye symptoms (4 items) and emotional (4 items). RQLQ(S)+12 responses are based on 7-point likert scale with responses ranging from 0 (not troubled) to 6 (extremely troubled). Individual items within RQLQ(S)+12 are equally

Trial name: LIBERTY ASTHMA QUEST Busse et al. Adv Ther (2018) 35:737–748	NCT number: NCT02414854
	weighted. The overall score is calculated as the mean score of all items. Higher scores indicated more health-related quality of life impairment (lower scores better).
Method of analysis	The annualized rate of severe exacerbation events was analyzed using a negative binomial regression model, with the total number of events occurring during the 52-week treatment period as the response variable, and the four treatment groups, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, and number of severe exacerbation events within 1 year prior to the study as covariates. Log-transformed observation duration was the offset variable. Change from baseline in continuous endpoints such as FEV1 and patient-reported outcomes were analyzed using a mixed-effects model with repeated measures (MMRM) Time-to-event endpoints were analyzed using a Cox regression model, with time to event as the dependent variable and treatment, age, number of asthma exacerbation events in the previous year, region (pooled country), baseline eosinophil strata, and baseline ICS dose level as covariates. The Kaplan–Meier method was used to estimate the probability of a patient experiencing an event. Descriptive statistics were used for demographic and clinical characteristics, pharmacodynamic variables, and for safety variables including AEs, vital signs and findings on physical examination, clinical laboratory testing, and ECG. Assuming an annualized exacerbation rate in the placebo group of 0.6, a sample size of approximately 1638 patients was estimated to provide 99% power (two-tailed a level of 0.05) to detect a 55% relative risk reduction (i.e., annualized rate of 0.27 for the dupilumab group) in the annualized rate of severe exacerbations. This sample size was also expected to provide 98% power to the second primary endpoint, capable of detecting a treatment difference of 0.15 L in change of FEV1 from baseline to week 12. In a population of this size, approximately 84 adolescent patients and 690 (42%) patients with a baseline blood eosinophil count of C 300 cells/ IL were expected to be randomized.

Trial name: LIBERTY ASTHA VENTURE. Rabe et al. N Engl J Med 2018;378:2475-85	NCT number: NCT02528214
Objective	To evaluate the efficacy of dupilumab, compared with placebo, for reducing the use of maintenance oral corticosteroids (OCS) in participants with severe steroid-dependent asthma.
Publications – title, author, journal, year	Rabe K et al: Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma N Engl J Med 2018;378:2475-85. DOI: 10.1056/NEJMoa1804093
Study type and design	A Randomized, Double-blind, Placebo-controlled Study
Sample size (n)	210 patients with oral glucocorticoid–treated asthma

Trial name: LIBERTY ASTHA VENTURE. Rabe et al. N Engl J Med 2018;378:2475-85	NCT number: NCT02528214

Main inclusion and exclusion criteria

Inclusion criteria:

Adult and adolescent (12 years of age or older) participants with a physician diagnosis of asthma for >=12 months, based on the Global Initiative for Asthma (GINA) 2014 guidelines and the following criteria:
Participants with severe asthma and a well-documented, regular prescribed treatment of maintenance corticosteroids in the 6 months prior to Visit 1 and using a stable OCS dose (ie, no change of OCS dose) for 4 weeks prior to Visit 1. Participants must be taking 5 to 35 mg/day of prednisone/prednisolone, or the equivalent, at Visit 1 and at the randomization visit. In addition, the participants must agree to switch to study-required prednisone/prednisolone as their OCS and use it per protocol for the duration of the study.

Existing treatment with high-dose inhaled corticosteroid (ICS; >500 mcg total daily dose of fluticasone propionate or equivalent) in combination with a second controller (ie, long-acting beta agonist [LABA], leukotriene receptor antagonist [LTRA]) for at least 3 months with a stable dose of ICS for >=1 month prior to Visit 1. In addition, participants requiring a third controller for their asthma are considered eligible for this study, and it should also be used for at least 3 months with a stable dose >= 1 month prior to Visit 1.

A forced expiratory volume in 1 second (FEV1) <80% of predicted normal for adults and <=90% of predicted normal for adolescents at Visit 1.

Evidence of asthma as documented by either: reversibility of at least 12% and 200 mL in FEV1 after the administration of 200 to 400 mcg (2 to 4 inhalations of albuterol/salbutamol or levalbuterol/levosalbutamol, or of a nebulized solution of albuterol/salbutamol or levalbuterol/levosalbutamol, if considered as a standard office practice) before randomization or documented in the 12 months prior to Visit 1 OR airway hyperresponsiveness (methacholine: provocative concentration that causes a positive reaction [PC20] of <8 mg/mL) documented in the 12 months prior to Visit 1.

Exclusion criteria:

- Participants <12 years of age or the minimum legal age for adolescents in the country of the investigative site, whichever is higher (for those countries where local regulations permit enrollment of adults only, participant recruitment will be restricted to those who were >=18 years of age).
- Participants who weighed <30.0 kg.
- Chronic obstructive pulmonary disease (COPD) or other lung diseases (eg, idiopathic pulmonary fibrosis, Churg-Strauss Syndrome, allergic bronchopulmonary aspergillosis, cystic fibrosis) which may impair lung function.
- Clinical evidence or imaging (eg, chest X-ray, computed tomography, magnetic resonance imaging) within 12 months of Visit 1 with clinically significant findings of lung disease(s) other than asthma, as per local standard of care.
- A participant who experiences a deterioration of asthma that results in emergency treatment or hospitalization within 4 weeks of Screening Visit 1.
- A participant who requires 12 puffs or more of rescue medication on any 1 day in the week prior to Visit 1.
- A participant who has experienced an upper or lower respiratory tract infection within the 4 weeks prior to screening.
- Current smoker or cessation of smoking within 6 months prior to Visit 1.
- Previous smoker with a smoking history >10 pack-years.
- Comorbid disease that might interfere with the evaluation of the investigational medicinal product.

Trial name: LIBERTY ASTHA VENTURE. Rabe et al. N Engl J Med 2018;378:2475-85	NCT number: NCT02528214
Intervention	Add-on dupilumab (at a dose of 300 mg) or placebo every 2 weeks for 24 weeks. After a glucocorticoid dose-adjustment period before randomization, glucocorticoid doses were adjusted in a downward trend from week 4 to week 20 and then maintained at a stable dose for 4 weeks
Comparator(s)	Dupilumab (at a dose of 300 mg) or placebo
Follow-up time	24 weeks
Is the study used in the health economic model?	Yes

Primary, secondary and exploratory endpoints	Percentage Reduction From Baseline in Oral Corticosteroids (OCS) Dose at Week 24 While Maintaining Asthma Control [Time Frame: Baseline, Week 24]Percentage reduction of OCS dose was calculated as (optimized OCS dose [mg/day] at baseline - final OCS dose at Week 24)/optimized OCS dose at baseline x 100. Result is presented as Least Squares Mean (Standard Error) percentage reduction from baseline derived from ANCOVA model with missing data multiply imputed. Supplementary Presentation of Primary Outcome Measure Data: Median Percentage Reduction From Baseline in Oral Corticosteroids Dose at Week 24 While Maintaining Asthma Control [Time Frame: Baseline, Week 24]The Primary Outcome Measure (Percentage Reduction From Baseline in Oral Corticosteroids Dose at Week 24 While Maintaining Asthma Control) is summarized above, as LS Mean (SE). Table below provides a supplementary presentation of the Primary Outcome Measure data; result is presented as median (inter-quartile range). Percentage reduction of OCS dose was calculated as (optimized OCS dose [mg/day] at baseline - final OCS dose at Week 24)/optimized OCS dose at baseline x 100. Secondary Outcome Measures : Percentage of Participants Achieving >= 50% Reduction in Oral Corticosteroids Dose at Week 24 While Maintaining Asthma Control [Time Frame: Week 24]Participants were classified according to the binary status of whether or not the 50% OCS dose reduction criterion was achieved at week 24. Percentage of Participants Achieving a Reduction in Oral Corticosteroids Dose to <5 mg/Day at Week 24 While Maintaining Asthma Control [Time Frame: Week 24]Participants were classified according to the binary status of whether or not the reduction of OCS dose to <5 mg/day was achieved at Week 24. Percentage of Participants Achieving Maximum Possible Reduction in Oral Corticosteroids Dose Per Protocol at Week 24 While Maintaining Asthma Control [Time Frame: Week 24]For all participants except those with baseline OCS dose at 35 mg/day, the maximum possible reduction corresponds to reduction to 0 mg/day (no longer requiring OCS). For participants starting with 35 mg/day at baseline, the maximum possible reduction is 32.5 mg/day (i.e. minimum dose per protocol is 2.5 mg). Percentage of Participants Who No Longer Required Oral Corticosteroids Dose at Week 24 While Maintaining Asthma Control [Time Frame: Week 24]Participants were classified according to the binary status of whether or not the participant still required OCS at Week 24 while maintaining asthma control.Absolute Reduction From Baseline in Oral Corticosteroids Dose at Week 24 While Maintaining Asthma Control [Time Frame: Baseline and Week 24]Absolute reduction was calculated by subtracting Week 24 value from baseline value. Other Outcome Measures: Annualized Rate of Severe Exacerbation Events During The 24-Week Treatment Period [Time Frame: Baseline to Week 24]A severe asthma exacerbation event was defined as a deterioration of asthma during the 24-week treatment period requiring: use of systemic corticosteroids for >=3 days (at least double the dose currently used); and/or hospitalization related to asthma symptoms or emergency room visit because of asthma requiring intervention with a systemic corticosteroid treatment. Annualized event rate was the total number of exacerbations that occurred during the treatment period divided by the total number of participant-years treated. Change From Baseline in Pre-Bronchodilator Forced Expiratory Volume in 1 Second (FEV1) at Weeks 12 and 24 [Time Frame: Baseline, Week 12 and Week 24]FEV1 was the volume of air exhaled in the first second of a forced expiration as measured by spirometer. Change From Baseline in Asthma Control Questionnaire 5-Question Version (ACQ-5) Score at Weeks 2, 4, 8, 12, 16, 20, and 24 [Time Frame: Baseline and at Weeks 2, 4, 8, 12, 16, 20, and 24]The ACQ-5 has 5 questions, reflecting top-scoring 5 asthma symptoms: woken at night by symptoms, wake in mornings with symptoms, limitation of daily activities, shortness of breath and wheeze. Participants were asked to recall how their asthma had been during previous week and to respond to each of 5 symptom questions on a 7-point scale ranged from 0 (no impairment) to 6 (maximum impairment). ACQ-5 total score was mean of scores of all 5

questions and, therefore, ranged from 0 (totally controlled) to 6 (severely uncontrolled). Higher score indicated lower asthma control.

Change From Baseline in Asthma Quality of Life Questionnaire (AQLQ) Global Score at Week 12 and Week 24 [Time Frame: Baseline, Week 12 and Week 24]AQLQ is a disease-specific, self-administered quality of life questionnaire designed to measure functional impairments that were most important to participants with asthma. AQLQ comprised of 32 items in 4 domains: symptoms (12 items), activity limitation (11 items), emotional function (5 items), environmental stimuli (4 items). Each item was scored on a 7-point likert scale (1=maximal impairment, 7=no impairment). The 32 items of the questionnaire were averaged to produce one overall quality of life score ranging from 1 (severely impaired) to 7 (not impaired at all). Higher scores indicate better quality of life.

Change From Baseline in European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L) Scores at Week 12 and Week 24 [Time Frame: Baseline, Week 12 and Week 24]EQ-5D-5L is a standardized health-related quality of life questionnaire developed by EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. EQ-5D consists of EQ-5D descriptive system and EQ visual analogue scale (VAS). EQ-5D descriptive system comprises of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The 5D-5L systems are converted into a single index utility score between 0 to 1, where higher score indicates a better health state. EQ-5D-5L-VAS records participant's self-rated health on a vertical VAS that allows them to indicate their health state that can range from 0 (worst imaginable) to 100 (best imaginable).

Change From Baseline in Hospital Anxiety and Depression Scale (HADS) Total Score at Week 12 and Week 24 [Time Frame: Baseline, Week 12 and Week 24]The HADS is a general scale to detect states of anxiety and depression already used and validated in asthma, which includes HADS-A and HADS-D subscales. The instrument is comprised of 14 items: 7 related to anxiety (HADS-A) and 7 to depression (HADS-D). Each item on the questionnaire is scored from 0-3. And, the total score is the sum of the scores of the 14 items ranging from 0 (no symptoms) to 42 (severe symptoms), with higher scores indicating higher anxiety/depression complains.

Change From Baseline in Sino Nasal Outcome Test-22 (SNOT-22) Global Score at Week 12 and Week 24 [Time Frame: Baseline, Week 12 and Week 24]The SNOT-22 is a validated measure of health related quality of life in sino nasal disease. It is a 22 item questionnaire with each item assigned a score ranging from 0-5. The total score may range from 0 (no disease) -110 (worst disease), lower scores represent better health related quality of life.

Trial name: LIBERTY ASTHA VENTURE. Rabe et al. N Engl J Med 2018;378:2475-85	NCT number: NCT02528214
Method of analysis	The primary end point was assessed with the use of an analysis of covariance model. The key secondary and other binary secondary end points were analyzed with the use of logistic-regression models. The annualized rate of severe exacerbations during the 24-week intervention period was analyzed with the use of a negative binomial regression model. A mixed effects model with a repeated-measures approach was used to analyze the changes from baseline in the FEV1 before bronchodilator use at various time points during the 24-week intervention period and the change from baseline in the ACQ-5 score at week 24. To control the overall type I error rate among the primary, key secondary, and the other binary secondary end points, multiple comparisons were controlled with the use of a prespecified hierarchical test procedure.

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

Table 97. Baseline characteristics of patients in tezepelumab studies included for the comparative analysis of efficacy and safety

Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety						
	Study name		Study name		Study name	
	NAVIGATOR		PATHWAY		SOURCE	
	PBO Q4W + SoC (n=531)	Teze 210 mg + SoC (n=528)	PBO Q4W + SoC (n=138)	Teze 210 mg + SoC (n=137)	PBO Q4W + SoC (n=76)	Teze 210 mg + SoC (n=74)
Age, years						
Mean (SD)	49.0 (15.9)	49.9 (16.3)	52.3 (11.7)	52.7 (12.7)	53.4 (11.9)	53.5 (12.1)
Sex						
Male, n (%)	194 (36.5)	193 (36.6)	44 (31.9)	50 (36.5)	31 (40.8)	25 (33.8)
OCS use						
Yes, n (%)	51 (9.6)	49 (9.3)	14 (10.1)	9 (6.6)	76 (100)	74 (100)
No, n (%)	480 (90.4)	479 (90.7)	124 (89.9)	128 (93.4)	0 (0)	0 (0)
Exacerbations in past 12 months[a]						
2,[b] n (%)	325 (61.2)	310 (58.7)	110 (79.7)	105 (76.6)	55 (72.4)	61 (82.4)
≥3, n (%)	206 (38.8)	218 (41.3)	28 (20.3)	32 (23.4)	21 (27.6)	13 (17.6)
Blood EOS, cells/µL	309 (58.2)	309 (58.5)	67 (48.6)	69 (50.4)	52 (68.4)	46 (62.2)
<300, n (%)	222 (41.8)	219 (41.5)	71 (51.4)	68 (49.6)	24 (31.6)	28 (37.8)
≥300, n (%)	138 (26.0)	138 (26.1)	-	-	24 (31.6)	27 (36.5)

	NAVIGATOR		PATHWAY		SOURCE	
	PBO Q4W + SoC (n=531)	Teze 210 mg + SoC (n=528)	PBO Q4W + SoC (n=138)	Teze 210 mg + SoC (n=137)	PBO Q4W + SoC (n=76)	Teze 210 mg + SoC (n=74)
<150, n (%)	171 (32.2)	171 (32.4)	-	-	28 (36.8)	19 (25.7)
150 to <300, n (%)	95 (17.9)	99 (18.8)	-	-	16 (21.1)	20 (27.0)
300 to <450, n (%)	127 (23.9)	120 (22.7)	-	-	8 (10.5)	8 (10.8)
≥450, n (%)						
FeNO, ppb[c]						
Mean (SD)	46.3 (44.7)	41.4 (36.3)	37.8 (39.7)	31.5 (29.8)	42.4 (37.4)	38.7 (40.8)
Allergic status[d]						
Allergic	341 (64.2)	339 (64.2)	80 (61.5)	77 (60.6)	34 (44.7)	25 (33.8)
Non-allergic	177 (33.3)	184 (34.8)	50 (38.5)	50 (39.4)	39 (51.3)	44 (59.5)
Unknown	13 (2.4)	5 (0.9)	-	-	3 (3.9)	5 (6.8)

Footnotes: *[a]An asthma exacerbation was defined as a worsening of asthma that either required treatment with a burst of SCS for at least three days or a single depot-injectable corticosteroid dose, or resulted in an ER visit which required SCS, or an inpatient hospitalisation due to asthma. For patients receiving a stable maintenance dose of OCS, a temporary increase for at least three consecutive days over and above the stable existing maintenance dose qualified as an exacerbation. [b]One patient in NAVIGATOR, enrolled in error, had one exacerbation in the year prior to the study and was included in the subgroup of subjects with two exacerbations in the year prior to the study. [c]High FeNO is indicative of type 2 inflammation. FeNO was recorded as the average of up to three measurements within 10% difference of each other. [d]In PATHWAY, allergic asthma was defined as a baseline positive IgE FEIA level to one or more region-specific allergens. In NAVIGATOR and SOURCE, allergic asthma was defined as a baseline positive perennial aeroallergen-specific IgE status (FEIA).*

Sources: *NAVIGATOR: Menzies-Gow 2021;(69) AstraZeneca/Amgen Data on File 2021;(70) PATHWAY: Corren 2017,(30) AstraZeneca/Amgen Data on File 2018;(71) SOURCE: AstraZeneca/Amgen Data on File 2021.(72)*

Table 98 Baseline characteristics of dupilumab studies, incl. the once used in the indirect treatment comparison

Studie	Female %	Etnicitet kaukasisk %	Alder gennemsnit år	BMI, gennemsnit kg/m²	Antal eksacerbationer indenfor seneste år, gennemsnit	LABA og andre 2nd controllers	ICS dosis (fluticasone propionate ækvivalente)	% som får OCS, daglig dosis gennemsnit prednisolonækvivalent	Præbronkodilator FEV1, gennemsnit L/gennemsnit % af forventet
dupilumab									
Wenzell 2016 (DRI125544) Corren 2019a (QoL) Corren 2019b (allergi subgruppe)	63 %	78 %	48,6	29,45	2,17	100 % Inklusions-kriterium	51% højdosis	Ikke angivet	1,84/ 60,8 %
Castro 2018 (QUEST) Castro 2019 (lungefunktion)	61,3-67,9 %	Ikke angivet	47,9-48,2	29,05-29,76	2,02-2,31	100 % Inklusions-kriterium	50,2-54,3 % højdosis	Ikke angivet	1,75-1,78/ 58,4 %
Rabe 2018 (VENTURE) Rabe 2019 (lungefunktion)	60-61 %	97-100	50,7-51,9	28,88-29,77	2,01-2,17	100 % inklusions-kriterium	Inklusionskriterium: > 500 µg	inklusionskriterium Før justeringsperiode. 11,83-11,79 mg/dag Efter justeringsperiode: 11,75-11,75 mg/dag	1,53-1,63 /52,2 %

Reference	n		Female (%)		Race White (%)		Mean age (years)		# exacerbations in last year		FEV1 (L)		FEV1 % predicted		Mean ACQ score		LABA use[a] (%)		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
Wenzel 2016 (main) (DRI12544) *Corren 2019a (QoL)*	150	158	64	66	76	75	51.0	49.0	1.9	2.3	1.79	1.82	61.2	61.0	2.7	2.7	LABA required		52	50	Not reported		39.3	39.0	361	342	416	419
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
Baseline characteristics has been adopted from dupilumab application to Medicine Council February 2020.

Comparability of patients across studies

Heterogeneity across studies in the ITC where observed across studies. Subgroup analysis and sensitivity analysis where performed to investigate the impact. Subgroup analyses focused on blood eosinophil count, FeNO level, number of exacerbations, and presence of allergic asthma was performed with more similar patient characteristics.

Based on the feasibility assessment and KEE feedback, differences in study characteristics were noted for studies informing the comparisons between tezepelumab and relevant biologics. Sensitivity analyses were conducted to assess the impact of removing such studies on NMA results. In addition, placebo response rates were compared across studies, as differences in placebo response may reflect important differences in measured and unmeasured confounders across study populations. Adjustment for differences in placebo response via meta-regression was considered since it can serve as a statistically efficient approach to account for cross trial differences.(73) For change from baseline in OCS dose, results from intermediate time-points in SOURCE [2020](26) were considered to account for any differences in assessment time-points.

Although the impact of these sources of heterogeneity was explored in subgroup and sensitivity analyses, NMA based on aggregate data is limited in its ability to fully adjust for potential treatment effect modifiers that may introduce bias in estimates of comparative efficacy. Hence, the results of ITC analyses leveraging IPD, including MAIC and STC, should also be considered when assessing the comparative efficacy of tezepelumab against other biologics used for moderate-to-severe asthma. More information regarding this can be shared upon request.

Comparability of the study populations with Danish patients eligible for treatment

Study populations are considered comparable to the Danish patients eligible for treatment.

Appendix D Efficacy and safety results across following studies: Tezepelumab: NAVIGATOR, PATHWAY, SOURCE, and Dupilumab: LIBERTY ASTHMA QUEST, VENTURE ASTHMA VENTURE, Wenzel S et al, LIBERTY ASTHMA TRAVERSE.

Definition, validity and clinical relevance of included outcome measures

Table 99 Definition, validity and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
Reduction in annualized asthma exacerbation rate, AAER	Annualized asthma exacerbation rate defined as exacerbation event deterioration of asthma (events per patient-year) at week 52 that require use of systemic corticosteroids, or hospital admission or emergency department visit during treatment and overall study periods which include follow-up	Standard outcome of respiratory studies. Widely accepted.	AAER is a key outcome for clinicians and patients
Reduction in exacerbations leading to hospitalization	Exacerbation event deterioration of asthma that require use of systemic corticosteroids, or hospital admission or emergency department visit during treatment and overall study periods which include follow-up. Severe exacerbations were defined as exacerbations that led to hospital admission for more than 24 hours	Standard outcome of respiratory studies. Widely accepted	Reduction in exacerbation leading to hospitalization is a key outcome for clinicians and patients
ACQ-score	The Asthma Control Questionnaire (ACQ)-5,-and 6 measures the adequacy of asthma control and change in asthma control. The ACQ assesses asthma and either rescue bronchodilator use or FEV_1. A score of ≤ 0.75 indicates adequately controlled asthma, while a score of ≥ 1.5 indicates asthma that is not well-controlled. The minimally important difference is a change in score of 0.5	Standard outcome of respiratory studies. Widely accepted	ACQ is a key outcome for clinicians and patients.
Change from baseline pre-bronchodilator FEV_1	Changes from baseline in the prebronchodilator and postbronchodilator FEV1 , forced expiratory volume in 1 second an increase in values indicates improved lung function; minimal clinically important difference, 100 to 200 ml	Standard outcome of respiratory studies. Widely accepted	Change from baseline pre-bronchodilator FEV_1 is a key outcome for clinicians and patients.
Change from baseline dose of OCS	The percentage reduction in the OCS, oral corticoid steroid, dose from baseline while asthma control was maintained. Asthma control considered to be maintained if no clinically significant event (on the basis of physician judgment) leads to an upward adjustment in the oral corticoid steroid dose occurred	Standard outcome of respiratory studies. Widely accepted	Change from baseline dose of OCS is a key outcome for clinicians and patients.

Table 100 Results per study

Table A3a Results of NAVIGATOR N Engl J Med 2021; 384:1800-1809 NCT03347279

				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**		
AAER at Week 52	Tezepelumab	528	0.93 (0.80; 1.07)	-1.17	-1.335; -0.969	<0.001*	RR=0.44 56%	0.37-0.53 47%, 63%;	0.001 0.001	A negative binomial regression model, with the total number of asthma exacerbations in a patient over the 52-week trial period used as a response variable.	Menzies-Gow 2021
	Placebo	531	2.10(1.84; 2.39)								
AAER at Week 52 EOS<300	Tezepelumab	309	1.02(0.84; 1.23)	-0.71	-0.934; -0.433	<0.001*	RR= 0.59	0.46; 0.75	0.001	See above.	Menzies-Gow 2021 Appendix
	Placebo	309	1.73(1.46; 2.05)								
AAER at Week 52 EOS<150	Tezepelumab	138	1.04(0.79; 1.37)	-0.66	-0.986; -0.306	0.013*	RR=0.61	0.42; 0.82	NR	See above	Menzies-Gow 2021 Appendix
	Placebo	138	1.70(1.32; 2.19)								
AAER at Week 52 EOS>300	Tezepelumab	219	0.79	-1.86	- 2.07; -1,596	<0.001*	RR= 0.30	0.22; 0.40	NR	See above	2021 Appendix
	Placebo	222	2.66								
FEV week 52	Tezepelumab	528	0.23+/-0.2	0.13 l	0.08; 0.18;	0.001	NR	NR	NR	Change from baseline in the prebronchodilator FEV1 MCID: 0.1L	Menzies-Gow 2021
	Placebo	531	0.09 +/-0.2								

Table A3a Results of NAVIGATOR N Engl J Med 2021; 384:1800-1809 NCT03347279											
AAER/Emergency ward or hospitalisations	**Tezepelumab**	**528**	**0.06(0.04; 0.09)**	-0.22	-0.246;-0.176	NR	RR: 0.21	0.12, 0.37	0.001	A negative binomial regression model, with the total number of asthma exacerbations in a patient over the 52-week trial period used as a response variable. RR calculated by AZ	Menzies-Gow 2021 Appendix
	Placebo	531	**0.28(0.20; 0.39)**								
Improved Asthma control ACQ-6 week 50	**Tezepelumab**	**528**	**86.2%**	NR	NR	NR	OR: 1.99	1.43, 2.76	NR	See table 23	Menzies-Gow 2021
	Placebo	531	**76.5%**								
ACQ-6 score vs baseline week 52	**Tezepelumab**	**528**	-1.55	-0.33	0.46; 0.20;	<0.001	NR	NR	NR	See table 23. CI calculated by AZ	Menzies-Gow 2021
	Placebo	531	**-1.22**								
AQLQ score vs baseline week 52	**Tezepelumab**	**528**	**1.49**	0.34	0.20; 0.47;	<0.001	NR	NR	NR	See table 23. CI calculated by AZ	Menzies-Gow 2021
	Placebo	531	**1.15**								
ASD score vs baseline week 52	**Tezepelumab**	**528**	**-0.71**	-0.12	-0.32; -0.12	<0.001*	RR: 0.21	0.12, 0.37	0.001	See table 23. CI and RR calculated by AZ	Menzies-Gow 2021
	Placebo	531	**-0.59**								

Table A3a Results of PATHWAY N Engl J Med 2017; 377:936-946 NCT02054130

				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**		
AAER at Week 52	Tezepelumab	137	0.20 (90 %: 0.14; 0.28)	-0.52(71%)	90 % CI (54%; 82%)	<0.001	RR=0.28	(0.19; 0.39)	NA	RR calculated by AstraZeneca CI absolute values calculated by AstraZeneca	NCT02054130
	Placebo	138	0.72 (90%:0.61; 0.86)								
AAER at Week 52 EOS<300	Tezepelumab	69	0.15 (0.07;0.28)	-0.65(81%)	-0.73; -0.432	<0.001	RR =0.19	(0.08; 0.46)	<0.001	RR calculated by AstraZeneca CI absolute values calculated by AstraZeneca	NCT02054130
	Placebo	67	0.80 (0.59;1.04)								
AAER at Week 52 EOS>400	Tezepelumab	43	0.20 (0.09;0.39)	0.66(73%)	(28%, 90%)	0.009	RR=0.19	(0.11; 0.33)	NA	RR calculated by AstraZeneca	NCT02054130 Suppl. Appendix
	Placebo	49	0.86 (0.62;1.16)								
FEV	Tezepelumab	137	NA	0.13 L	(0.03, 0.23)	0.009	NR	NR	NR	Change from baseline in the prebronchodilator FEV1 MCID: 0.1L	NCT02054130
	Placebo	138	NA								
ER/hospi-talisations	Tezepelumab	69	0.03(0.01; 0.08)	-0.15	-0.173; -0.076	NR	RR=0.15	0.04; 0.58	0.005	RR calculated by AstraZeneca	NCT02054130
	Placebo	67	0.18(0.12; 0.27)								
Improved Asthma control	Tezepelumab	137	81.8%	12.2%	2.2%; 22.2%	NR	OR: 1.94	1.08, 3.47	NR	RR calculated by AstraZeneca	NCT02054130
	Placebo	138	69.6%				RR=0.60	0.39; 0.93			

Table A3a Results of PATHWAY N Engl J Med 2017; 377:936-946 NCT02054130											
ACQ-6 week 50											
ACQ-6 score vs baseline week 48	Tezepelumab	44	-1.20	-0.29	-0.56, -0.01	0.039	NA	NA	NA	See table 23. CI calculated by AstraZeneca	NCT02054130
	Placebo	53	-0.91								
AEs(all events	Tezepelumab	137	90(65.7%/0.657)	-0.003%	-0,105; 0.119%	NA	RR=0.996	(0.84; 1.18)	NA	See table 23	NCT02054130
	Placebo	138	91(65.9%/0.659)							RR and CI intervals calculated by AstraZeneca	
SAE (all events) grade 3-5	Tezepelumab	137	32(23.7%/0.237)	-0.012%	-0.093; 0,108	NA	RR=0.95	(0.62; 1.44)	NA	RR and CI intervals calculated by AstraZeneca	RR calculated by AstraZeneca
	Placebo	138	34(24.6%/0.246)								

Table A3a Results of SOURCE Wechsler et al. Respiratory Research (2020) 21:264 with update Lancet Respir Med 2022; 10: 650–60

				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		
Cumulative OCS reduction week 48	Tezepelumab	76	NR	NR	NR	NR	OR: 1.28	0.69, 2.35	0.434	A proportional odds (ordinal logistic regression) model, with the ordered percentage reduction category number (1–5) at week 48 as the response variable. Treatment and region are included as factors in the model. Baseline OCS dose is included as a continuous (linear) covariate in the model The following proportions were assumed for placebo: • Category 1 (90–100% reduction): 10% of patients • Category 2 (75–<90% reduction): 10% of patients • Category 3 (50–<75% reduction): 15% of patients • Category 4 (>0–<50% reduction): 15% of patients • Category 5 (no reduction or an increase): 50% of patients The minimal detectable odds ratio still being significant with the above assumptions was 1·86.	NCT03406078
	Placebo	74	NR								

Table A3a Results of SOURCE Wechsler et al. Respiratory Research (2020) 21:264 with update Lancet Respir Med 2022; 10: 650–60											
AAER at week 48 ITT	Tezepelumab	74	1.38(0.98,1.95)	-0.62	-1,120; 0.180	NR	RR=0.69	(0.44; 1.09)		See above	NCT03406078(Post hoc appendix)
	Placebo	76	2.00(1.46,2.74)								
AAER at Week 48 EOS<300	Tezepelumab	46	1.71(1.14;2.57)	0.18	-0.55; 1,454	NR	RR=1.12	(0.64, 1.95)		See above	NCT03406078 (Post hoc appendix)
	Placebo	52	1.53(1.04;2.26)								
AAER at Week 52 EOS<150	Tezepelumab	27	2.27(1.35,3.81)	0.59	-0.605; 3.142	NR	RR=1.35	(0.64, 2.87)		CI for absolute values calculated by AstraZeneca	NCT03406078
	Placebo	24	1.68(0.96,2.95)								
AAER at Week 52 EOS>300	Tezepelumab	28	0.87(0.48,1.56)	-2.087	2,528; -1,088	NR	RR= 0.29	(0.14, 0.63)	NR	CI for absolute values calculated by AstraZeneca	NCT03406078 (Post hoc appendix)
	Placebo	24	2.94(1.79,4.84)								
FEV	Tezepelumab	65	0.21L(SE 0.05)	0.26 L	0.13, 0.39	NR	NR	NR	NR	CI for absolute values calculated by AstraZeneca	NCT03406078
	Placebo	64	-0.04L(SE 0.05)								
ER/hospitalizations	Tezepelumab	76	0.16(0.06;0.44)	-0.115	-0.227; 0.230	NR	RR: 0.59	0.19, 1.82	0.361	CI for absolute values calculated by AstraZeneca	NCT03406078
	Placebo	74	0.28(0.13;0.58)								
	Tezepelumab	66	-0.87(SE 0.13)	-0.37	-0.71, -0.02	NR	NR	NR	NR		NCT03406078

Table A3a Results of SOURCE Wechsler et al. Respiratory Research (2020) 21:264 with update Lancet Respir Med 2022; 10: 650–60				
ACQ-6 score vs baseline week 48	Placebo	68	-0.51(SE 0.12)	CI for absolute values calculated by AstraZeneca

Table A3a Results of randomized, double-blind, placebo-controlled, dose-ranging study to evaluate dupilumab in patients with moderate to severe uncontrolled asthma. NTC 01854047

				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**		
Annualised rate of severe exacerbation(EOS ≥150 cells/µL)	**Dupi**	**120**	0.290 (0.159; 0.529)	-0.762	-1.215; -0.273	**0.0004**	**0.276**	**0.128; 0.595**	0.001	A negative binomial regression model,including the total number of events occurring during the double-blind treatment period as the response variable; treatment group, baseline blood EOS strata, pooled countries or regions, and number of asthma events in the year before the study as covariates; and log transformed treatment duration as the offset variable[a]	EPAR
	Placebo	127	1.052 (0.693; 1.598)								
Proportion of patients with 0 exacerbations in the 24-week treatmentperiod (ITT)	**Dupi**	148	91.2 (86.7; 95.8)	NR	NR	NR	NR	NR	NR		
	Placebo	158	74.1 (67.2; 80.9)								

Table A3a Results of randomized, double-blind, placebo-controlled, dose-ranging study to evaluate dupilumab in patients with moderate to severe uncontrolled asthma. NTC 01854047

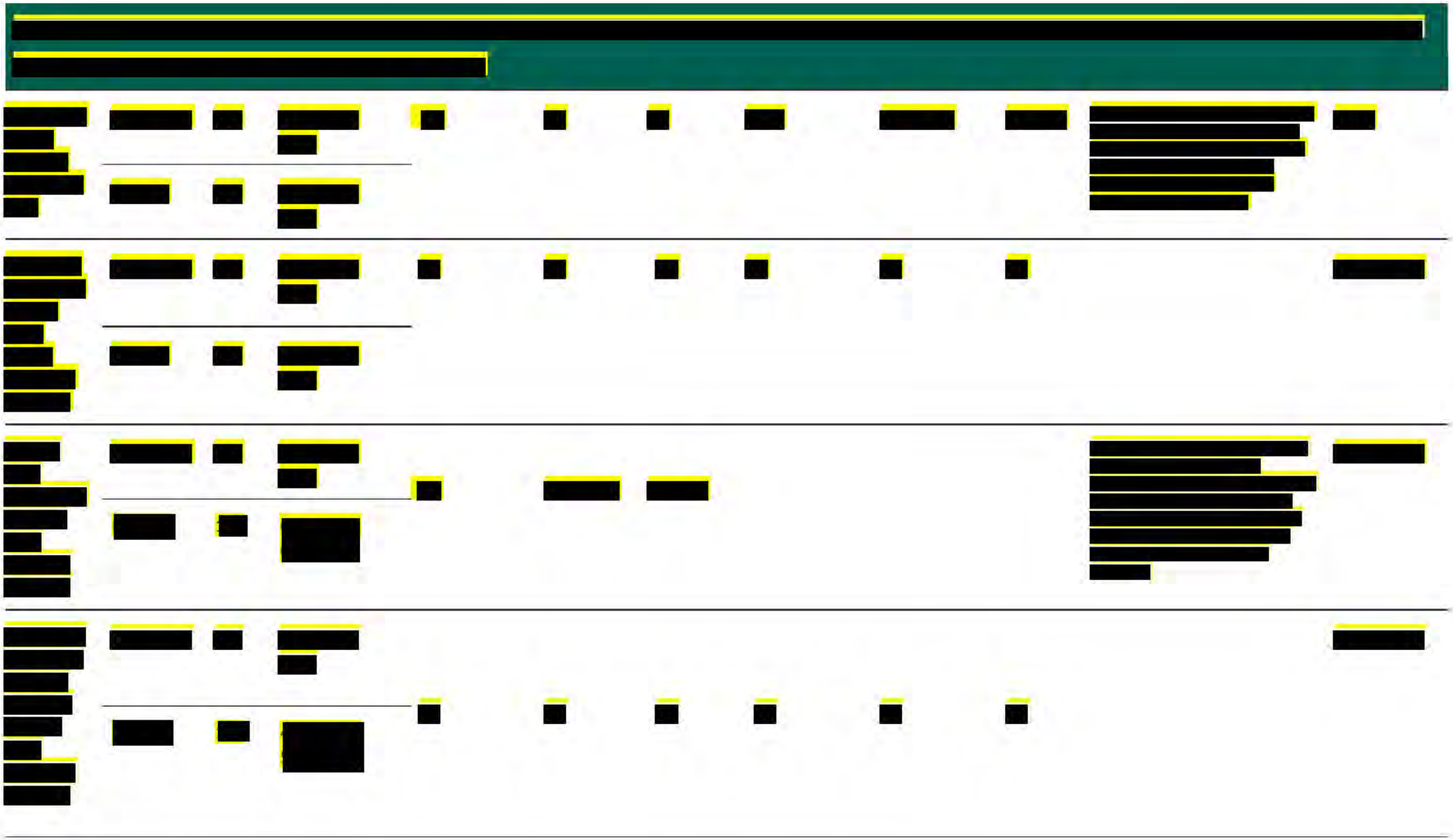
Change from baseline to week 12 in FEV1 (L) (EOS ≥150 cells/µL)	Dupi	120	0.32 (0.242; 0.398)	0.23	0.13; 033	<0.0001	NR	NR	NR	A mixed-effects model with a repeated measures approach. The model included change from baseline to week 12 as response variables, factors (fixed effects) for treatment, baseline blood EOS strata,pooled countries or regions, visit, treatment-by-visit interaction, baseline value, and baseline-by-visit interaction[b]	
	Placebo	127	0.09 (0.012; 0.168)								
Change from baseline to week 24 in asthma control(**ACQ-5**) (EOS ≥150 cells/µL)	Dupi	108	-1.55 (-1.726; -1.374)	-0.48	0.72; -0.23	0.0002	NR	NR	NR	A mixed-effects model with a repeated measures approach. The model included change from baseline to week 12 as response variables, factors (fixed effects) for treatment, baseline blood EOS strata, pooled countries or regions, visit, treatment-by-visit interaction, baseline value, and baseline-by-visit interaction[b]	
	Placebo	100	-1.07 (-1.246; -0.894)								
Change from baseline to week 24 in quality of life (AQLQ)(EOS ≥150 cells/µL)	Dupi	106	**1.27 (1.07; 1.46)**	-0.49	0.24; 0.75	0.0002	NR	NR	NR	See above	
	Placebo	100	**0.78 (0.58; 0.98)**								
Annualised days sick leave due to severe exacerbation	Dupilumab	150	0.613[c]	NR	NR	<0.0001	NR	NR	NR	Poisson model with the total number of events onset between first dose date and last dose date +14 days as the response variable, treatment, pooled countries/regions, and number of asthma events because of the study as covariates, and log-transformed standardised (in years)	
	Placebo	158	2.238[c]								

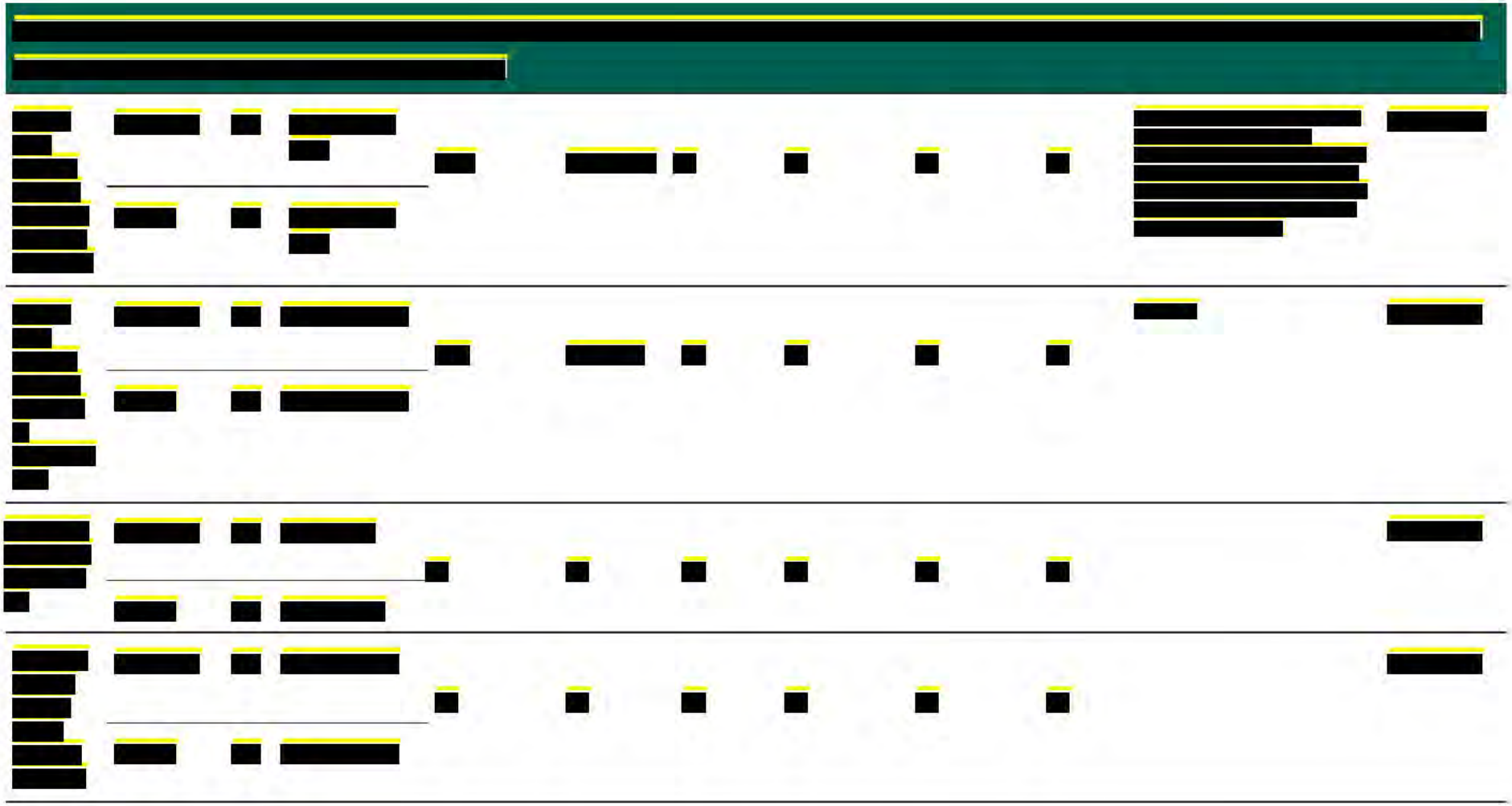
Table A3a Results of randomized, double-blind, placebo-controlled, dose-ranging study to evaluate dupilumab in patients with moderate to severe uncontrolled asthma. NTC 01854047

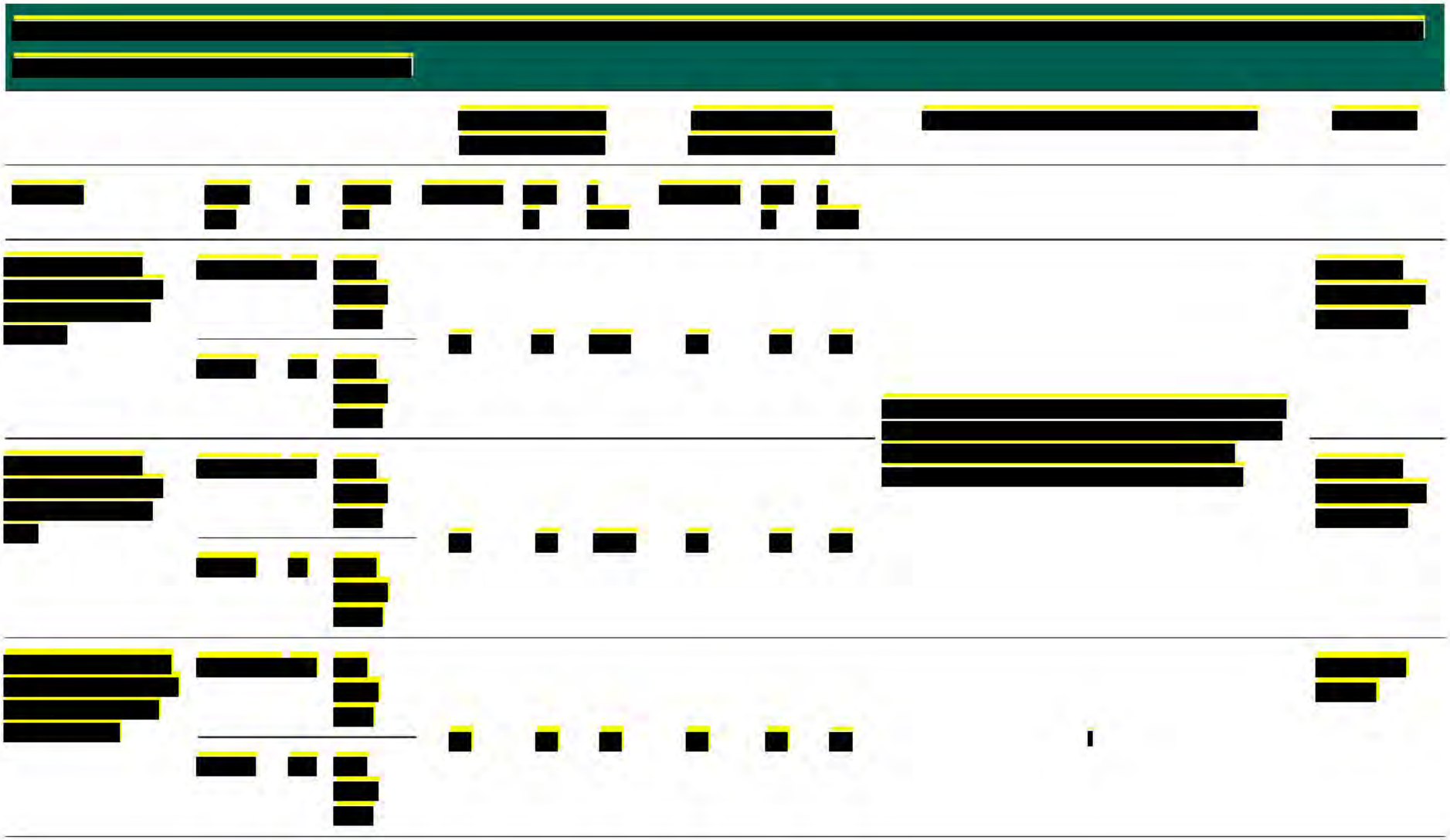
event(days /year) (ITT)										treatment duration as an offset variable
Proportion of patients with SAE (total) (%)	Dupilumab	148	6.8 (2.7; 10.8)	NR	NR	NR	NR	NR	NR	Wenzel 2016 table 4
	Placebo	158	5.7 (2.1; 9.3)							
Proportion of patients discontinued from the study (%)	Dupilumab	148	7.4 (3.2; 11.7)	NR	NR	NR	NR	NR	NR	Wenzel 2016 table 4
	Placebo	158	7.6 (3.5; 11.7)							

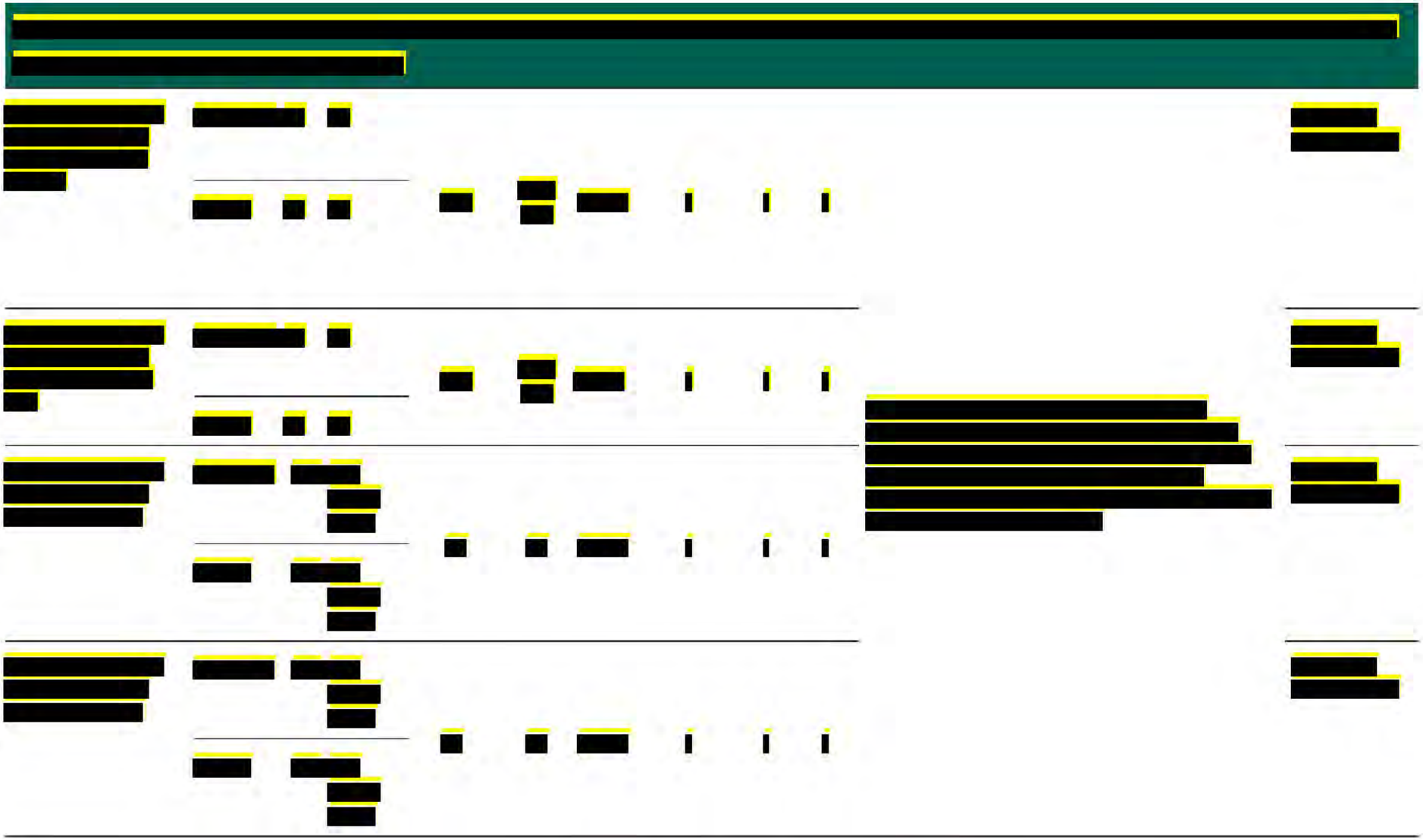
For patients who prematurely discontinued the study drug, events occurring during the treatment period were included and the analysis adjusted for the treatment duration; ᵇ FEV1 measurements collected from systemic
corticosteroid start date to systemic corticosteroid end date plus 30 days for each exacerbation episode were excluded from the primary analysis to reduce the confounding effect of systemic corticosteroids. For patients
discontinuing treatment before week 12, off -treatment FEV1 values were excluded in the primary analysis; ᶜ No measures of variability reported
Proportion of patients with ≥200 mL improvement in FEV1 was not reported.

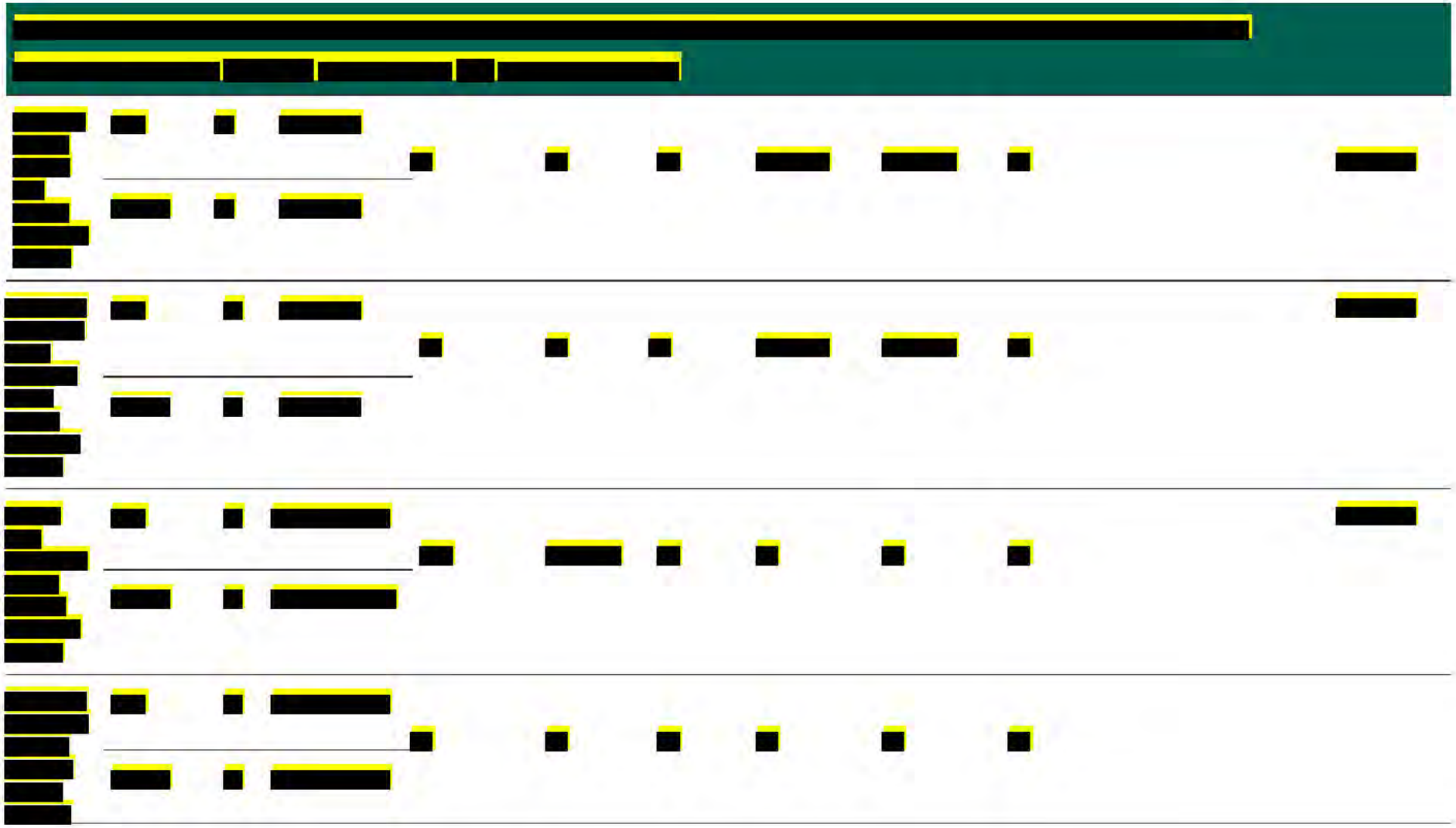
[redacted]

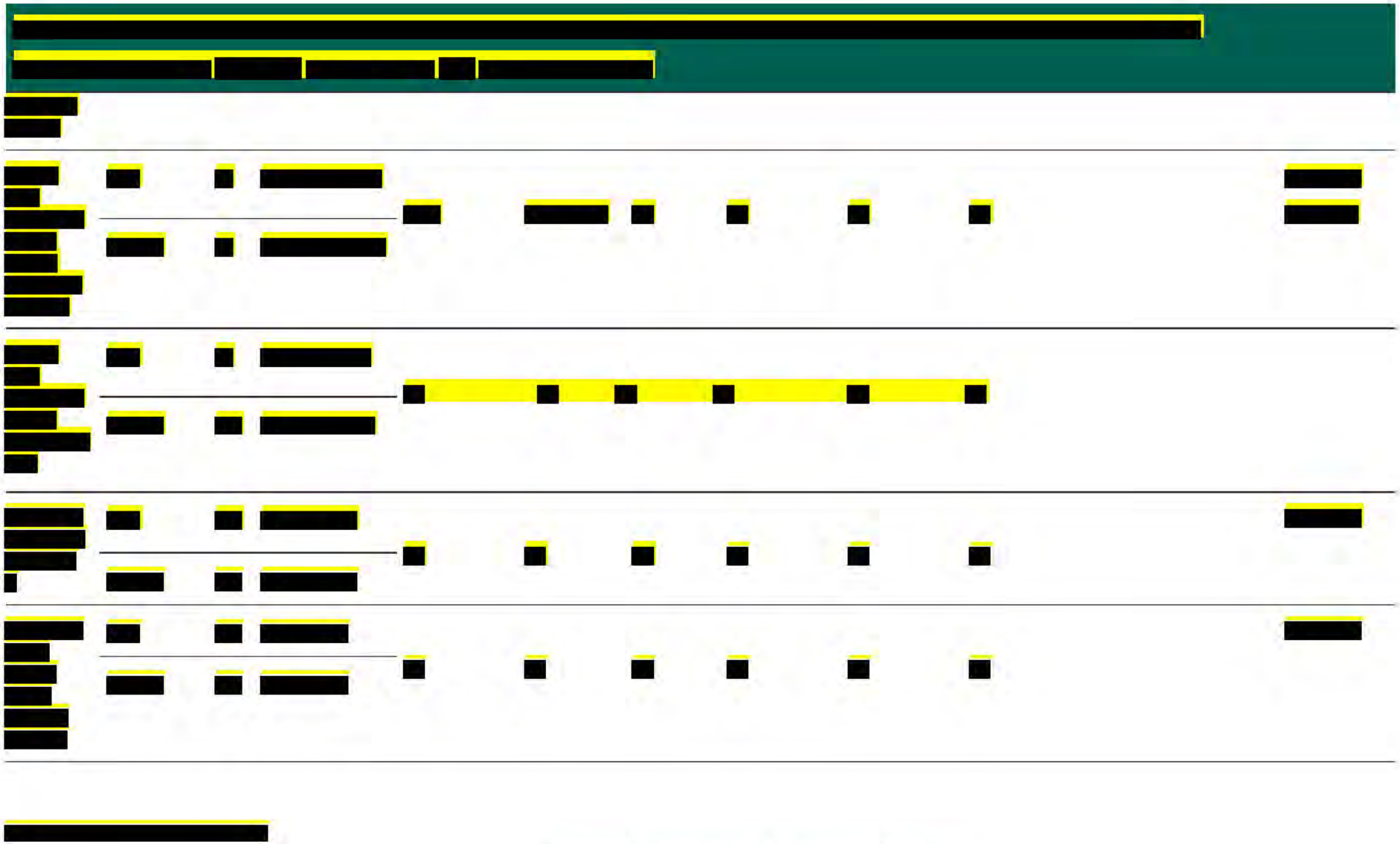


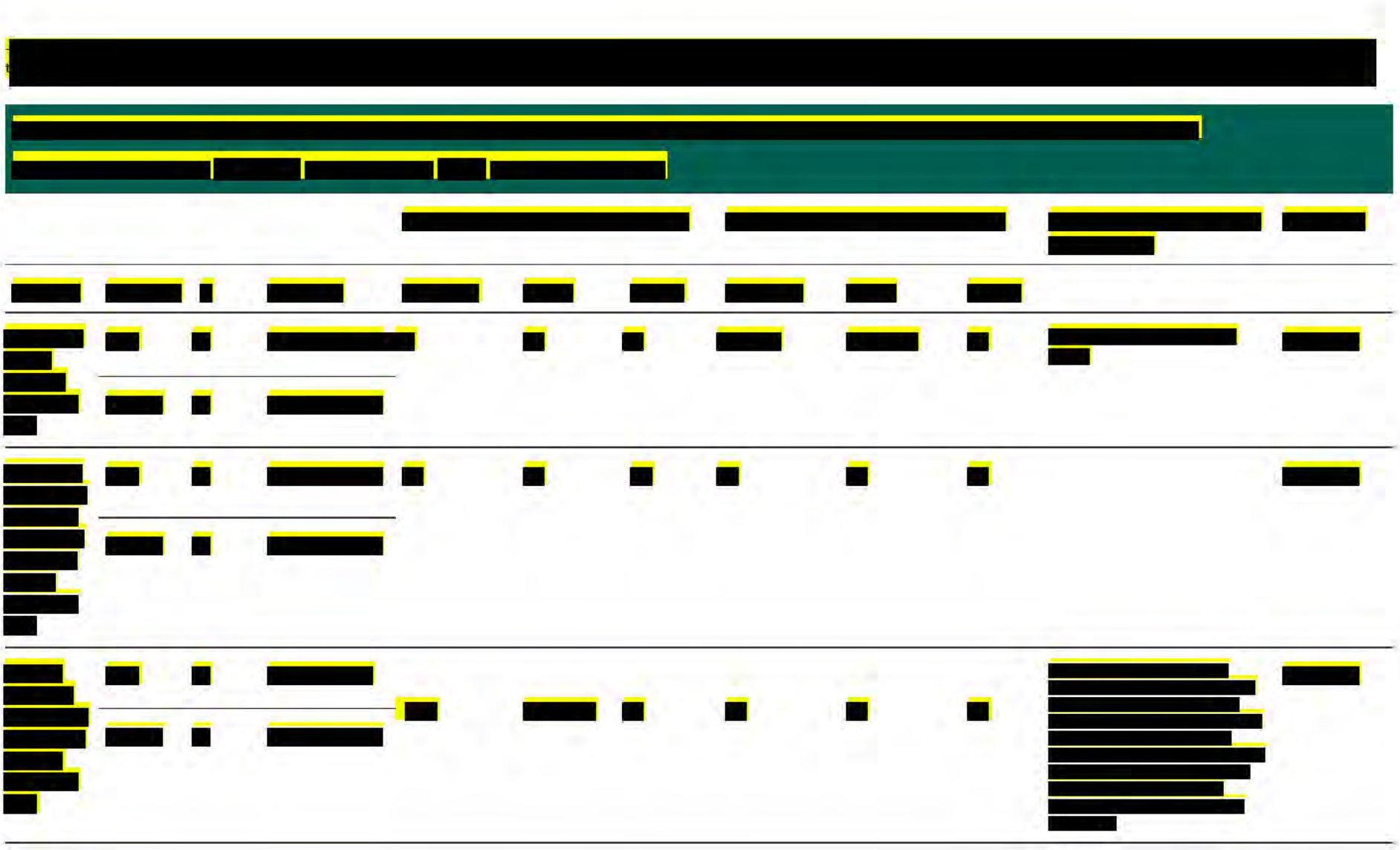


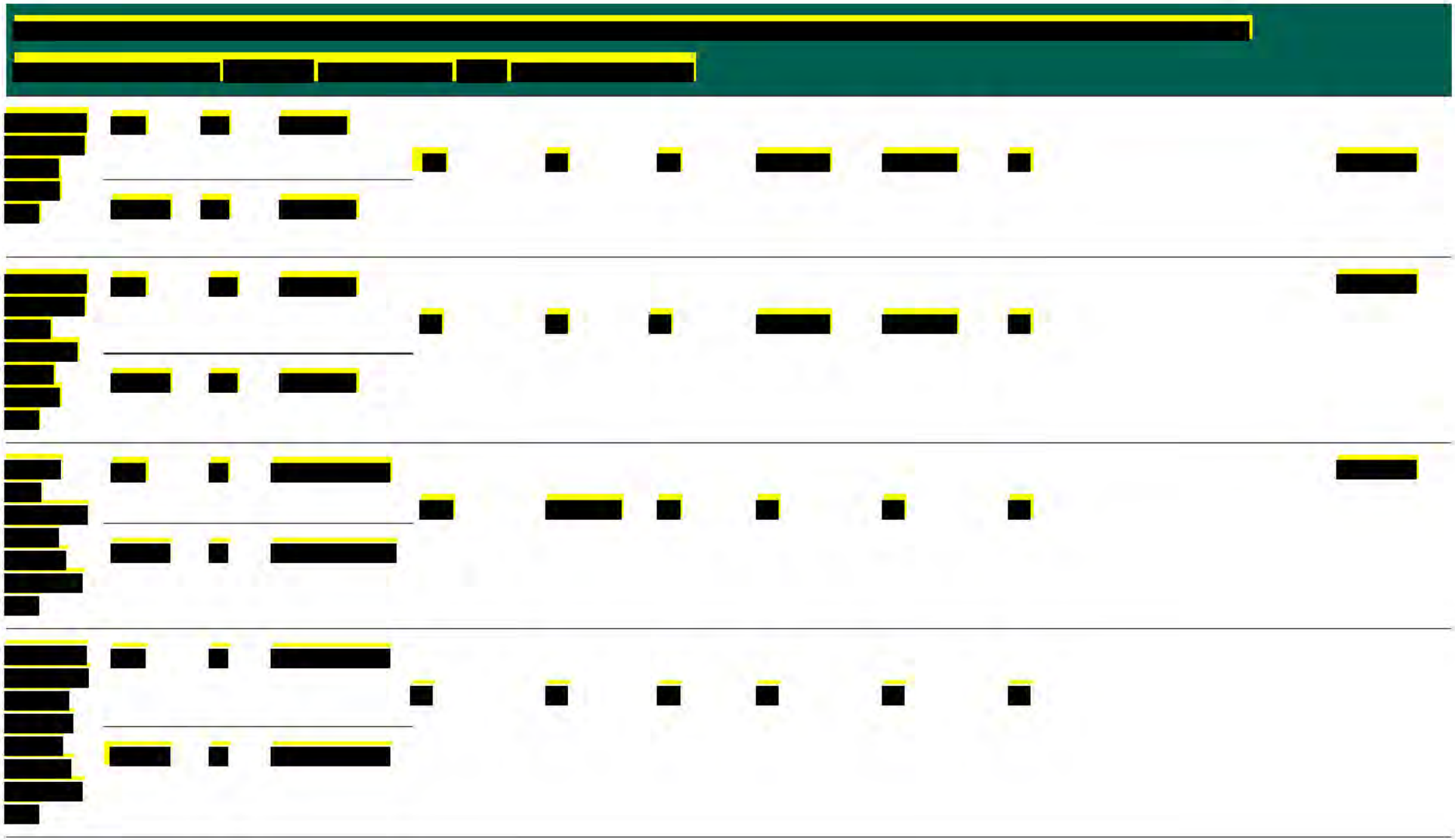


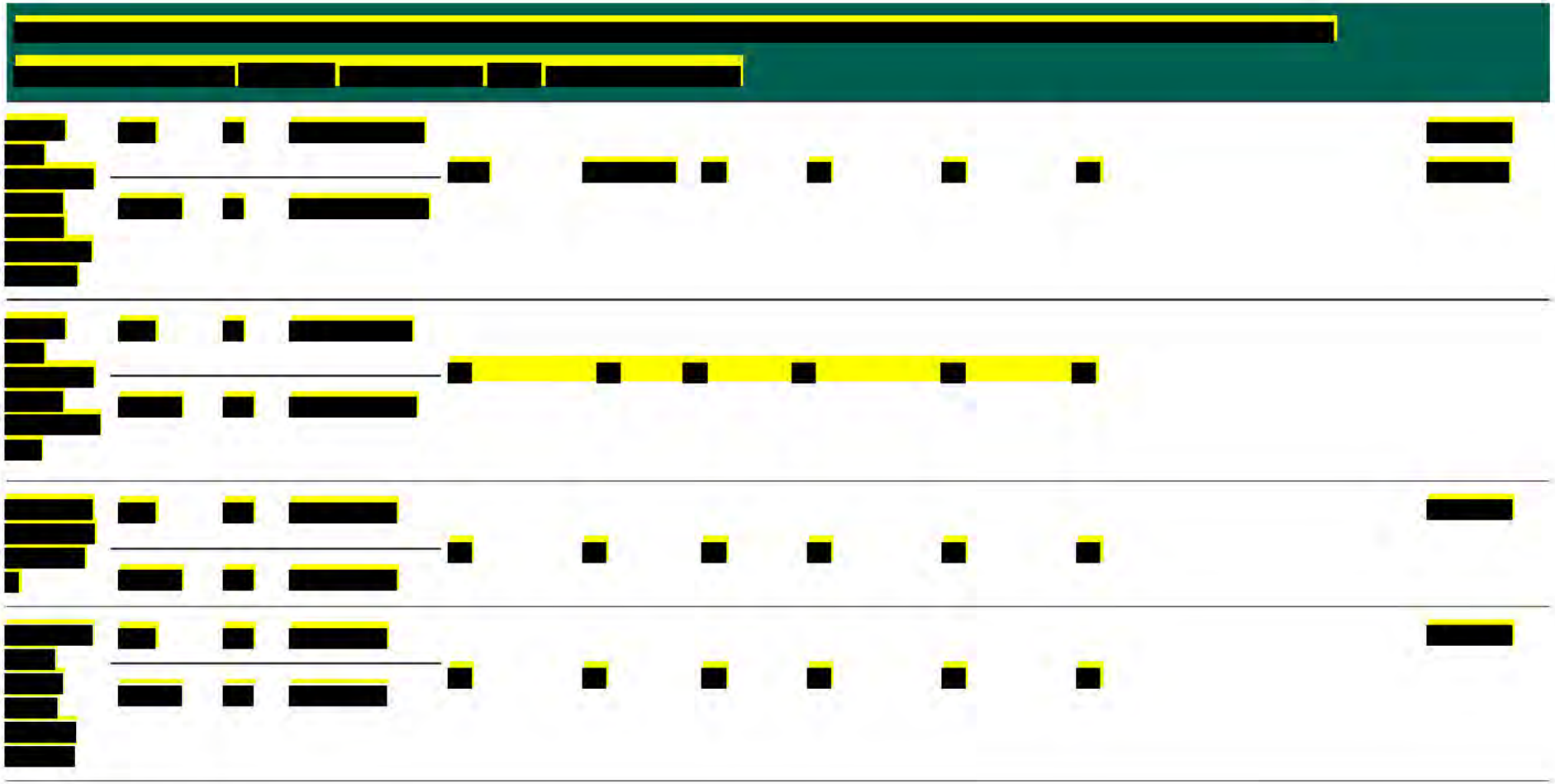












Appendix E Safety data for intervention and comparator(s)

Intervention

Across the NAVIGATOR, PATHWAY and SOURCE trials, tezepelumab was well tolerated in patients with severe asthma and demonstrated a similar safety profile to optimised SoC alone (Table 25). Furthermore, tezepelumab was associated with low discontinuation rates in patients with severe, uncontrolled asthma across phenotypes and irrespective of biomarkers.

Table 101 Summary of adverse events in tezepelumab trials population

	NAVIGATOR		PATHWAY			SOURCE	
	PBO Q4W + SoC (n=531)	Teze 210 mg Q4W + SoC (n=528)	PBO Q2W + SoC (n=138)	Teze + SoC (all doses) (n=412)	Teze Q4W 210 mg + SoC (n=137)	PBO Q4W + SoC (n=76)	Teze 210 mg Q4W + SoC (n=74)
≥1 event, n (%)	422 (79.5)	407 (77.1)	91 (65.9)	272 (66.0)	90 (65.7)	65 (85.5)	53 (71.6)
Product-related anaphylaxis, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Product-related death, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)[a]	0 (0.0)	0 (0.0)	0 (0.0)
≥1 serious event[a], n (%)	70 (13.2)	46 (8.7)	18 (13.0)	40 (9.7)	13 (9.5)	16 (21.1)	11 (14.9)
≥1 event leading to treatment discontinuation, n (%)	19 (3.6)	11 (2.1)	1 (0.7)	5 (1.2)	2 (1.5)	2 (2.6)	2 (2.7)
Most common AEs in NAVIGATOR[c]							
Nasopharyngitis, n (%)	113 (21.3)	112 (21.2)	16 (11.6)	53 (12.9)	19 (13.9)	19 (25.0)	11 (14.9)
Upper respiratory tract infection, n (%)	84 (15.8)	58 (11.0)	-	-	-	7 (9.2)	9 (12.2)
Headache, n (%)	44 (8.3)	43 (8.1)	6 (4.3)	22 (5.3)	11 (8.0)	8 (10.5)	3 (4.1)
Asthma, n (%)	56 (10.5)	25 (4.7)	50 (36.2)	100 (24.3)	27 (19.7)	13 (17.1)	7 (9.5)
Bronchitis, n (%)	31 (5.8)	24 (4.5)	7 (5.1)	22 (5.3)	5 (3.6)	3 (3.9)	4 (5.4)

Footnotes: *Colour coding used only to differentiate results from each trial. Patients were counted once for each category regardless of the number of events.* [a]*One patient treated with teze 70 mg + SoC died due to an event of cerebrovascular accident; this death was judged by the investigator as being related to investigational product.* [b]*A serious adverse event was defined as an event that resulted in death, was life threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or clinically significant disability or incapacity, was an important medical event, or resulted in a congenital anomaly or resulted in a birth defect (in the offspring of the patient).* [c]*Shown are the five most commonly occurring events in the group of patients who received tezepelumab in NAVIGATOR.*
Abbreviations: *PBO placebo; SAS safety analysis set; SoC standard of care; teze tezepelumab.*
Sources *PATHWAY Corren 2017;(30) NAVIGATOR AstraZeneca/Amgen Data on File 2021;(70) SOURCE AstraZeneca/Amgen Data on File 2021.(72)*

Adverse events of special interest (AESIs)

TSLP is a central regulator of the immune response to inhaled environmental insults.(74) By blocking TSLP at the top of the inflammatory cascade, tezepelumab has the potential to suppress multiple inflammatory pathways and immune mechanisms, with a possible effect on the immune response to infectious agents. However, the mechanisms by which tezepelumab suppresses inflammatory pathways remains unclear.(75) Therefore, the effect of treatment with tezepelumab + SoC on the incidence of severe infections was of special interest. However, trial results show that the incidence of severe infections (defined as infections requiring treatment with systemic antiviral medications, intravenous antibiotics, or medications for helminth parasitic infection; or infections requiring permanent treatment discontinuation) was low overall and similar between the tezepelumab 210 mg Q4W + SoC and PBO Q4W + SoC groups in NAVIGATOR (46 [8.7%] and 44 [8.3%] patients, respectively) and in PATHWAY (4 [2.9%] and 4 [2.9%], respectively). (64, 76) In SOURCE, the incidence of severe infections in the on-treatment period was lower in the tezepelumab 210 mg Q4W + SoC group (n=4 [5.4%]) than the PBO Q4W + SoC group (n=7 [9.2%]).[72] Furthermore, an in vitro study on human cells demonstrated that tezepelumab therapy improves host tolerance to viruses by decreasing inflammatory alarmins or cytokines without affecting anti-viral resistance.(75) The incidence of cancer did not differ between the treatment groups in NAVIGATOR (n=4 in both groups, with one event being causally related to tezepelumab);(70) in SOURCE, there was one event of incidence of malignancy reported in the tezepelumab 210 mg Q4W + SoC group (1/74 [1.4%]) and no events in the PBO Q4W + SoC group. The event was not considered to be causally related to the treatment.(72) Injection site reactions occurred in 3.6% and 2.6% of patients treated with tezepelumab 210 mg Q4W + SoC and PBO Q4W + SoC, respectively, in NAVIGATOR.(70) In SOURCE, no injection-site reactions were reported in the tezepelumab 210 mg Q4W + SoC group; one patient in the PBO Q4W + SoC group (1/76 [1.3%]) experienced three injection site reactions during the on-study period.(72)

Immunogenicity

At or after baseline, the anti-drug antibody (ADA) prevalence (defined as the proportion of patients who tested positive for ADA at any point in time) reported in the NAVIGATOR trial was 26 (4.9%) and 44 (8.3%) in the tezepelumab 210 mg Q4W + SoC and PBO Q4W + SoC groups, respectively.[70] Similarly, in SOURCE, a total of five (3.3%) patients were found to have ADAs at any time point (including baseline); this included three (4.1%) patients in the tezepelumab 210 mg Q4W + SoC group, and two (2.6%) patients in the PBO Q4W + SoC group.(70) Presence of ADAs in both tezepelumab 210 mg Q4W + SoC- and PBO Q4W + SoC-treated patients indicated that the ADA observations were likely not due to tezepelumab 210 mg Q4W + SoC treatment.(70)

Safety and tolerability conclusions

Across NAVIGATOR, PATHWAY and SOURCE, tezepelumab 210 mg Q4W + SoC demonstrated a favorable benefit/risk profile in severe, uncontrolled asthma patients with no clinically meaningful differences in safety versus optimised SoC alone.(26, 30, 87) (30, 75, 79) Tezepelumab 210 mg Q4W + SoC was associated with low discontinuation rates; furthermore, despite blocking TSLP at the top of the inflammatory cascade, treatment with tezepelumab 210 mg Q4W + SoC was not associated with any increase in the incidence of severe infections. Tezepelumab 210 mg Q4W + SoC was also well tolerated, with a low ADA prevalence in patients treated with tezepelumab. (26, 27)

Table 102: Summary of adverse events in dupilumab trial population (Ref: QUEST)

	PBO, 1.14 ml (n=313)	Dupi 200 mg (n=631)	PBO, 2.00 ml (n=321)	Dupi, 300 mg (n=632)	Combined PBO (n=634)	Combined Dupi) (n=1263)
≥1 event, n (%)	257 (82.1)	508 (80.5)	270 (84.1)	515 (81.5)	527 (83.1)	1023 (81.0)
Any adverse event leading to death, n (%)	3 (1.0)	1 (0.2)	0	4 (0.6)	3 (0.5)	5 (0.5)
≥1 serious event[a], n (%)	26 (8.3)	49 (7.8)	27 (8.4)	55 (8.7)	53 (8.4)	104 (8.2)
≥1 event leading to treatment discontinuation, n (%)	19 (6.1)	19 (3.0)	10 (3.1)	44 (7.0)	29 (4.6)	63 (5.0)
Most common AEs in NAVIGATORc						
Viral Upper respiratory tract infection, n (%)	**60 (19.2)**	**119 (18.9)**	**64 (19.9)**	**111 (17.6)**	**124 (19.6)**	**230 (18.2)**
Upper respiratory tract infection	**37 (11.8)**	**69 (10.9)**	**49 (15.3)**	**77 (12.2)**	**86 (13.6)**	**146 (11.4)**
Bronchitis, n (%)	**47 (15)**	**73 (11.6)**	**42 (13.1)**	**38 (6.0)**	**89 (14.0)**	**74 (5.9)**
Influenza, n (%)	**29 (9.3)**	**36 (5.7)**	**22 (6.9)**	**26 (4.1)**	**51 (8.0)**	**62 (4.9)**
Sinusitis, n (%)	**27 (8.6)**	**36 (5.7)**	**29 (9.0)**	**19 (3.0) 40 (6.3)**	**56 (8.8)**	**36 (2.9)**
Headache, n (%)	**26 (8.3)**	**46 (7.3)**	**25 (7.8)**		**29 (4.6)**	**86 (6.8)**

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Appendix F Comparative analysis of efficacy and safety

The NMA is described below. Further details can be seen in a separate document.

Five outcomes, informed by clinical importance, payer relevance and availability in comparator publications, were considered in the NMA:

Reduction in AAER;

Reduction in exacerbations leading to hospitalisation;

Change from baseline in ACQ score (it was assumed that results of ACQ-5, ACQ-6 and ACQ-7 are similar and comparable based on expert opinion,(77, 78) adding uncertainty to the networks);

Change from baseline in pre-bronchodilator FEV_1;

Change from baseline in the OCS dose by predefined mutually exclusive reduction categories (reduction of ≥50%, 50–75%, 75–90%, 90–100%).

For each of the five clinical outcomes, evidence networks were developed and a Bayesian NMA was performed according to established methods (based on those outlined in the National Institute for Health and Care Excellence [NICE] Decision Support Unit [DSU] Technical Support Documents [TSDs]).(79)

[redacted]

Table 103 Pairwise comparisons from the NMA between tezepelumab and other currently approved biologics

Outcome	Outcome type	MCID (favouring tezepelumab)	Comparator (reference) treatment					
			Benralizumab	Dupilumab 200 mg	Dupilumab 300 mg	Omalizumab	Mepolizumab	Reslizumab
Reduction in AAER	RR (95% CrI); <1 favours tezepelumab	≤0.80 (20% reduction)	0.63 (0.35, 1.09)	0.84 (0.45, 1.56)	0.84 (0.45, 1.56)	0.6 (0.35, 1.01)	0.82 (0.43, 1.49)	0.82 (0.43, 1.49)
Reduction in exacerbations leading to hospitalisation	RR (95% CrI); <1 favours tezepelumab	NA[a]	0.35 (0.08, 1.16)	0.36 (0.07, 1.59)	NA	0.40 (0.10, 1.55)	0.54 (0.13, 2.00)	0.29 (0.07, 1.08)
ACQ score	LSMean difference in CfB (95% CrI); <0 favours tezepelumab	≤ -0.5	-0.01 (-0.30, 0.28)	0.04 (-0.29, 0.36)	-0.06 (-0.38, 0.27)	0.16 (-0.19, 0.51)	0.1 (-0.24, 0.45)	-0.06 (-0.34, 0.27)

pre-BD FEV_1 (L)	LSMean difference in CfB (95% CrI); >0 favours tezepelumab	≥ +0.2 L	0.02 (-0.07, 0.11)	-0.01 (-0.10, 0.08)	0.0 (-0.09, 0.09)	0.08 (-0.01, 0.18)	0.02 (-0.07, 0.12)	0.01 (-0.08, 0.09)
OCS dose reduction by ≥50%	OR (95% CrI); >1 favours tezepelumab	NA	0.38 (0.14 to 1.07)	NA	0.36 (0.14 to 0.93)	NA	0.54 (0.20 to 1.47)	NA
OCS dose reduction by 50–75%[a]	OR (95% CrI); >1 favours tezepelumab	NA	0.37 (0.16 to 0.85)	NA	0.42 (0.19 to 0.93)	NA	0.54 (0.23 to 1.30)	NA
OCS dose reduction by 75–90%[a]	OR (95% CrI); >1 favours tezepelumab)	NA	0.38 (0.16 to 0.86)	NA	0.42 (0.20 to 0.93)	NA	0.54 (0.24 to 1.30)	NA
OCS dose reduction by 90–100%[a]	OR (95% CrI); >1 favours tezepelumab	NA	0.38 (0.16 to 0.86)	NA	0.42 (0.19 to 0.93)	NA	0.54 (0.23 to 1.30)	NA

Footnotes: *No results were statistically significant at p=0.05. Results coloured green numerically favour tezepelumab with a clinically important difference where a MCID is available; results coloured grey indicate that the outcome is not associated with a MCID; all other results demonstrate comparable effectiveness of tezepelumab (i.e. no clinically important difference).* [a]*No MCID is available for the reduction in exacerbations leading to hospitalisation, but any reduction may be considered clinically relevant.* [b]*The reciprocal of odds ratios with tezepelumab as the comparator treatment have been calculated to present odds ratios with the other biologics as the comparator treatment.*

Abbreviations: *ACQ Asthma Control Questionnaire; BD bronchodilator; CfB change from baseline; CrI credible interval; FEV_1 forced expiratory volume in one second; LSMean least squares mean; MCID clinically important difference; NA no data available; NMA network meta-analysis; OCS oral corticosteroid; OR odds ratio; RR rate ratio; TBC to be confirmed.*

Source *AstraZeneca/Amgen Data on File 2021.(78)*

Key clinically relevant subpopulations, reflecting the diversity of approved indications and reimbursement criteria for the comparator products, were of interest. In addition, subgroup analyses allowed comparison of biologics in populations with more similar patient characteristics (ie, asthma-control related characteristics and biomarkers). Subgroup analyses focused on blood eosinophil count, FeNO level, number of exacerbations, and presence of allergic asthma. Subgroup results were commonly reported in the included trials as relative effects vs. placebo for each outcome (i.e., unlike the ITT population, trials did not report arm-specific data for subgroups). Relative effect estimates were therefore used for all subgroup analyses. The result from the subgroup analyses are presented in Table 28 and shows that in the patient population with high blood EoS levels, tezepelumab was statistically significant better than omalizumab and benralizumab in reducing annual asthma exacerbations. In the patient population with low blood EoS levels, tezepelumab was statistically significant better than dupilumab 300mg in reducing annual asthma exacerbations.

No subgroup analyses were conducted for AAER leading to hospitalizations due to the lack of available data.

For the outcome of change from baseline in ACQ score, tezepelumab and mepolizumab were statistically significantly better than benralizumab for the patient population with high blood EoS levels.

For the outcome of change from baseline in the OCS dose, the were no statistically significant difference between Tezspire and the other currently approved biologics. When studying the change from baseline in OCS dose by ≥50%, both tezepelumab and dupilumab showed statistically significant improvements compared to mepolizumab.

Table 104 Overview of subgroup analysis results.

Subgroup of Interest	Definition	Findings/comparisons with primary analysis
Reduction in AAER		
High blood EoS level	≥150 cells/µL	Tezepelumab was statistically significantly better than omalizumab (RR 0.63 (95%CI 0.43 to 0.94)) and benralizumab (RR 0.63 (95%CI 0.49 to 0.82)).
Low blood EoS level	<150 cells/µL	Tezepelumab was statistically significantly better than dupilumab 300mg (RR 0.55 (95%CI 0.39 to 0.79)).
Change from baseline in ACQ Score		
High blood EoS level	≥150 cells/µL	Tezepelumab and mepolizumab were statistically significantly better than benralizumab (RR -0.23 (95%CI -0.40 to -0.04) and (RR -0.32 (95%CI -0.53 to -0.11), respectively).
Low blood EoS level	<150 cells/µL	No statistically significant differences between biologics.
Change from baseline in pre-bronchodilator FEV		
High blood EoS level	≥150 cells/µL	No statistically significant differences between biologics.
Low blood EoS level	<150 cells/µL	No statistically significant differences between biologics
Change from baseline in the OCS dose		
Change from baseline in OCS dose by ≥50%, ≥75%, or ≥90%		
High blood EoS level	≥150 cells/µL	No statistically significant differences between biologics.
Change from baseline in OCS dose by ≥50%		
High blood EoS level	≥150 cells/µL	No statistically significant differences between biologics.

Summary of comparative effectiveness

The presented NMAs support the conclusion that biologic interventions for severe uncontrolled asthma are associated with significantly improved AAER, AAER leading to hospitalization, ACQ score, FEV_1 and OCS reduction as compared with placebo.

Additionally, the results suggest that there are no clear differences between biologic comparators for any of the outcomes. However, these results should be interpreted with caution given the extent of clinically important heterogeneity in patient populations and trial methods across studies.
The impact of these sources of heterogeneity was explored in subgroup analyses, showing advantages of Tezspire, especially in the reduction of AAER.

ITC feasibility assessment

NMA requires that the studies being assessed are clinically and methodologically (e.g., study design, population characteristics, outcome definitions) similar.(80) The similarity between studies can impact the validity of the findings (i.e., failure to account for differences can lead to misleading comparisons of treatment effect).(73) Therefore, the RCTs identified in the systematic literature review (3 tezepelumab and 36 comparator RCTs) were assessed for comparability. The full assessment included a review of study characteristics, inclusion criteria, exclusion criteria, distribution of potential treatment effect modifiers, and outcome definitions.
In terms of study characteristics, key differences were observed for study phase, blinding, and type of comparator across studies. Specifically, all RCTs, except for five omalizumab RCTs (Ayres [2004](54), NCT0056746 [2007](81), and EXALT [2011](47), Hoshino [2012](45), and QUALITX [2012](82)), were double-blinded and placebo-controlled. For inclusion criteria, key differences were observed for blood eosinophil count, OCS use, skin prick test, and IgE levels. For treatment effect modifiers, key differences were also observed in blood eosinophils and number of exacerbations in the past 12 months. Furthermore, RCTs designed to assess OCS-reduction exclusively enrolled patients that were OCS users, whereas the percentage of OCS users in the remaining RCTs with available data ranged from 0% to 40%. Based on feedback from KEEs, the differences in blood eosinophils, number of exacerbations, and OCS users were significant because they could impact the validity of NMA results. For outcome definitions, assessment time-points varied between studies for all outcomes. The differences for AAER were considered important by KEEs therefore the analysis for this outcome accounted for variation in follow up time.

Conclusion

The NMAs presented in this report support the conclusion that biologic interventions for moderate-to-severe uncontrolled asthma are associated with significantly improved AAER, AAER leading to hospitalization, ACQ score, FEV_1, and OCS reduction as compared with placebo. Additionally, the results suggest that there are no clear differences between biologic comparators for any of the outcomes. However, these results should be interpreted with caution given the extent of clinically important heterogeneity in patient populations and trial methods across studies. Although the impact of these sources of heterogeneity was explored in subgroup and sensitivity analyses, NMA based on aggregate data is limited in its ability to fully adjust for potential treatment effect modifiers that may introduce bias in estimates of comparative efficacy.

Appendix G – Extrapolation

There were no extrapolation done for the relative effects. The probability inputs were applied per cycle as a cyclical probability throughout the model time horizon.

Appendix H – Literature search for HRQoL data

A literature search for HRQoL was not performed since the utility estimates for the health states "Uncontrolled asthma" and "Controlled asthma" were derived from the NAVIGATOR and SOURCE trials. The utility decrements for the exacerbations events were applied by published decrements by Lloyd et al. (2007). Since several assessments of biologic treatments for patients with severe uncontrolled asthma have used the published utility decrement by Lloyd et al, these decrements were assessed as the most propriate to also use in the Tezepelumab cost-effectiveness analyses. See Section 8 for more details.

Appendix I Mapping of HRQoL data

As described in Section 8.3, EQ-5D-5L responses from the NAVIGATOR and SOURCE trials where each of the unique health states were valued based on the Danish preference weights, published by Jansen et al.

Appendix J Probabilistic sensitivity analyses

Table 105. Parameters in the probabilistic sensitivity analysis for the High FeNO population

Baseline Characteristics					
Parameter Group	**Parameter**	**Arm**	**Mean**	**SE**	**Distribution**
Demographics	Age (Years)	All	50,24	0,64	Normal
	Proportion Male		0,401	0,021	Beta

Transition Probabilities					
Parameter Group	**Parameter**	**Arm**	**Mean**	**SE**	**Distribution**
Tezepelumab Pre-Assessment With OCS	Controlled Asthma -> Uncontrolled Asthma	Tezepelumab	0,12000	0,02653	Beta
	Controlled Asthma -> Controlled Exacerbation		0,02000	0,01143	Beta
	Uncontrolled Asthma -> Controlled Asthma		0,13472	0,02458	Beta
	Uncontrolled Asthma -> Uncontrolled Exacerbation		0,07772	0,01927	Beta
	Controlled Exacerbation -> Controlled Asthma		1,00000	0,00000	Beta
	Controlled Exacerbation -> Uncontrolled Asthma		0,00000	0,00000	Beta
	Uncontrolled Exacerbation -> Controlled Asthma		0,13636	0,07317	Beta
	Uncontrolled Exacerbation -> Uncontrolled Asthma		0,59091	0,10482	Beta
Tezepelumab Pre-Assessment Without OCS	Controlled Asthma -> Uncontrolled Asthma	Tezepelumab	0,08114	0,00719	Beta
	Controlled Asthma -> Controlled Exacerbation		0,02358	0,00400	Beta
	Uncontrolled Asthma -> Controlled Asthma		0,21380	0,01190	Beta
	Uncontrolled Asthma -> Uncontrolled Exacerbation		0,08670	0,00816	Beta
	Controlled Exacerbation -> Controlled Asthma		0,75000	0,07655	Beta

	Controlled Exacerbation -> Uncontrolled Asthma		0,25000	0,07655	Beta
	Uncontrolled Exacerbation -> Controlled Asthma		0,25000	0,04092	Beta
	Uncontrolled Exacerbation -> Uncontrolled Asthma		0,61607	0,04595	Beta
Tezepelumab Post-Assessment With OCS	Controlled Asthma -> Uncontrolled Asthma	Tezepelumab	0,12081	0,02670	Beta
	Controlled Asthma -> Controlled Exacerbation		0,03061	0,01151	Beta
	Uncontrolled Asthma -> Controlled Asthma		0,14286	0,02645	Beta
	Uncontrolled Asthma -> Uncontrolled Exacerbation		0,10426	0,01910	Beta
	Controlled Exacerbation -> Controlled Asthma		1,00000	0,00000	Beta
	Controlled Exacerbation -> Uncontrolled Asthma		0,00000	0,00000	Beta
	Uncontrolled Exacerbation -> Controlled Asthma		0,17647	0,09246	Beta
	Uncontrolled Exacerbation -> Uncontrolled Asthma		0,58824	0,11936	Beta
Tezepelumab Post-Assessment Without OCS	Controlled Asthma -> Uncontrolled Asthma	Tezepelumab	0,07988	0,00731	Beta
	Controlled Asthma -> Controlled Exacerbation		0,02650	0,00353	Beta
	Uncontrolled Asthma -> Controlled Asthma		0,22396	0,01266	Beta
	Uncontrolled Asthma -> Uncontrolled Exacerbation		0,08969	0,00715	Beta
	Controlled Exacerbation -> Controlled Asthma		0,78261	0,08601	Beta
	Controlled Exacerbation -> Uncontrolled Asthma		0,21739	0,08601	Beta
	Uncontrolled Exacerbation -> Controlled Asthma		0,31343	0,05667	Beta
	Uncontrolled Exacerbation -> Uncontrolled Asthma		0,62687	0,05909	Beta
SoC With OCS	Controlled Asthma -> Uncontrolled Asthma	SoC	0,17424	0,03302	Beta
	Controlled Asthma -> Controlled Exacerbation		0,15909	0,03184	Beta

	Uncontrolled Asthma -> Controlled Asthma		0,10630	0,01934	Beta
	Uncontrolled Asthma -> Uncontrolled Exacerbation		0,15748	0,02286	Beta
	Controlled Exacerbation -> Controlled Asthma		0,68182	0,09930	Beta
	Controlled Exacerbation -> Uncontrolled Asthma		0,22727	0,08935	Beta
	Uncontrolled Exacerbation -> Controlled Asthma		0,15217	0,05296	Beta
	Uncontrolled Exacerbation -> Uncontrolled Asthma		0,67391	0,06912	Beta
SoC Without OCS	Controlled Asthma -> Uncontrolled Asthma	SoC	0,14910	0,01098	Beta
	Controlled Asthma -> Controlled Exacerbation		0,07787	0,00826	Beta
	Uncontrolled Asthma -> Controlled Asthma		0,17331	0,01048	Beta
	Uncontrolled Asthma -> Uncontrolled Exacerbation		0,17101	0,01043	Beta
	Controlled Exacerbation -> Controlled Asthma		0,55556	0,04994	Beta
	Controlled Exacerbation -> Uncontrolled Asthma		0,19192	0,03958	Beta
	Uncontrolled Exacerbation -> Controlled Asthma		0,21724	0,02422	Beta
	Uncontrolled Exacerbation -> Uncontrolled Asthma		0,47931	0,02934	Beta
SoC With OCS 2nd year and on	Controlled Asthma -> Uncontrolled Asthma	SoC	0,17424	0,03302	Beta
	Controlled Asthma -> Controlled Exacerbation		0,24189	0,07714	Beta
	Uncontrolled Asthma -> Controlled Asthma		0,10630	0,01934	Beta
	Uncontrolled Asthma -> Uncontrolled Exacerbation		0,23944	0,06186	Beta
	Controlled Exacerbation -> Controlled Asthma		0,68182	0,09930	Beta
	Controlled Exacerbation -> Uncontrolled Asthma		0,22727	0,08935	Beta
	Uncontrolled Exacerbation -> Controlled Asthma		0,15217	0,05296	Beta

	Uncontrolled Exacerbation -> Uncontrolled Asthma		0,67391	0,06912	Beta
SoC Without OCS 2nd year and on	Controlled Asthma -> Uncontrolled Asthma	SoC	0,14910	0,01098	Beta
	Controlled Asthma -> Controlled Exacerbation		0,11840	0,03138	Beta
	Uncontrolled Asthma -> Controlled Asthma		0,17331	0,01048	Beta
	Uncontrolled Asthma -> Uncontrolled Exacerbation		0,26002	0,02728	Beta
	Controlled Exacerbation -> Controlled Asthma		0,55556	0,04994	Beta
	Controlled Exacerbation -> Uncontrolled Asthma		0,19192	0,03958	Beta
	Uncontrolled Exacerbation -> Controlled Asthma		0,21724	0,02422	Beta
	Uncontrolled Exacerbation -> Uncontrolled Asthma		0,47931	0,02934	Beta

Exacerbations

Parameter Group	Parameter	Arm	Mean	SE	Distribution
Distribution Controlled With OCS	Proportion OCS Burst	Tezepelumab	1,000	0,000	Beta
		SoC	0,893	0,058	Beta
	Proportion A&E Visit	Tezepelumab	0,000	0,000	Beta
		SoC	0,071	0,049	Beta
	Proportion Hospitalisation	Tezepelumab	0,000	0,000	Beta
		SoC	0,036	0,035	Beta
Distribution Controlled Without OCS	Proportion OCS Burst	Tezepelumab	0,921	0,044	Beta
		SoC	0,915	0,026	Beta
	Proportion A&E Visit	Tezepelumab	0,026	0,026	Beta
		SoC	0,034	0,017	Beta
	Proportion Hospitalisation	Tezepelumab	0,053	0,036	Beta
		SoC	0,051	0,020	Beta
	Proportion OCS Burst	Tezepelumab	1,000	0,000	Beta

Distribution Uncontrolled With OCS		SoC	0,836	0,050	Beta
	Proportion A&E Visit	Tezepelumab	0,000	0,000	Beta
		SoC	0,055	0,031	Beta
	Proportion Hospitalisation	Tezepelumab	0,000	0,000	Beta
		SoC	0,109	0,042	Beta
Distribution Uncontrolled Without OCS	Proportion OCS Burst	Tezepelumab	0,919	0,025	Beta
		SoC	0,860	0,018	Beta
	Proportion A&E Visit	Tezepelumab	0,073	0,023	Beta
		SoC	0,056	0,012	Beta
	Proportion Hospitalisation	Tezepelumab	0,008	0,008	Beta
		SoC	0,084	0,015	Beta
Duration Cost Component Controlled (Weeks)	OCS Burst	Tezepelumab	1,29	0,14	Normal
		SoC	1,27	0,15	Normal
	A&E Visit	Tezepelumab	1,29	0,14	Normal
		SoC	1,27	0,15	Normal
	Hospitalisation	Tezepelumab	1,14	0,14	Normal
		SoC	3,06	1,08	Normal
Duration Cost Component Uncontrolled (Weeks)	OCS Burst	Tezepelumab	1,25	0,07	Normal
		SoC	1,23	0,05	Normal
	A&E Visit	Tezepelumab	1,25	0,07	Normal
		SoC	1,23	0,05	Normal
	Hospitalisation	Tezepelumab	1,64	0,34	Normal
		SoC	2,90	0,58	Normal
Duration Utility Component Controlled (Weeks)	OCS Burst	Tezepelumab	1,29	0,14	Normal
		SoC	1,27	0,15	Normal
	A&E Visit	Tezepelumab	1,29	0,14	Normal
		SoC	1,27	0,15	Normal
	Hospitalisation	Tezepelumab	1,14	0,14	Normal

		SoC	3,06	1,08	Normal
Duration Utility Component Uncontrolled (Weeks)	OCS Burst	Tezepelumab	1,25	0,07	Normal
		SoC	1,23	0,05	Normal
	A&E Visit	Tezepelumab	1,25	0,07	Normal
		SoC	1,23	0,05	Normal
	Hospitalisation	Tezepelumab	1,64	0,34	Normal
		SoC	2,90	0,58	Normal
Mortality Risk OCS Burst	Age 18-44	All	0,00019	0,00003	Beta
	Age 45+		0,00312	0,00024	Beta
Mortality Risk A&E Visit	Age 18-44	All	0,00197	0,00034	Beta
	Age 45+		0,03189	0,00242	Beta
Mortality Risk Hospitalisation	Age 18-24	All	0,03189	0,00319	Beta
	Age 25-34		0,00000	0,00000	Beta
	Age 36-44		0,00058	0,00006	Beta
	Age 45-54		0,00080	0,00008	Beta
	Age 55-64		0,00080	0,00008	Beta
	Age 65+		0,00302	0,00030	Beta

OCS

Parameter Group	Parameter	Arm	Mean	SE	Distribution
Baseline OCS	Proportion on OCS	All	0,120	0,015	Beta
	OCS Dose (mg/Day)		11,27	0,65	Normal
OCS Sparing Timing	Sparing Week	All	52,00	0,00	Normal
OCS Sparing Reduction	Proportion with No Reduction	Tezepelumab	0,222	0,069	Beta
		SoC	0,186	0,059	Beta
	Proportion with >0% - <50%	Tezepelumab	0,000	0,000	Beta
		SoC	0,163	0,056	Beta
	Proportion with 50% - <75%	Tezepelumab	0,139	0,058	Beta

			SoC	0,186	0,059	Beta
	Proportion with 75% - <90%		Tezepelumab	0,056	0,038	Beta
			SoC	0,047	0,032	Beta
	Proportion with 90% - 100% (Discontinuation)		Tezepelumab	0,583	0,082	Beta
			SoC	0,419	0,075	Beta
	Dose Reduction Scaling		All	Medium		
Adverse Event Prevalence Type-2 Diabetes Mellitus	>0.0 - <0.5mg		All	0,00629	0,00063	Beta
	0.5 - <2.5mg			0,01368	0,00137	Beta
	2.5 - <5.0mg			0,02005	0,00200	Beta
	5.0 - <7.5mg			0,02457	0,00246	Beta
	7.5 - <15.0mg			0,04235	0,00423	Beta
	≥15.0mg			0,07950	0,00795	Beta
Adverse Event Prevalence Osteoporosis	>0.0 - <0.5mg		All	0,00200	0,00020	Beta
	0.5 - <2.5mg			0,00660	0,00066	Beta
	2.5 - <5.0mg			0,01531	0,00153	Beta
	5.0 - <7.5mg			0,02043	0,00204	Beta
	7.5 - <15.0mg			0,03319	0,00332	Beta
	≥15.0mg			0,01176	0,00118	Beta
Adverse Event Prevalence Glaucoma	>0.0 - <0.5mg		All	0,00136	0,00014	Beta
	0.5 - <2.5mg			0,00281	0,00028	Beta
	2.5 - <5.0mg			0,00381	0,00038	Beta
	5.0 - <7.5mg			0,00759	0,00076	Beta
	7.5 - <15.0mg			0,00468	0,00047	Beta
	≥15.0mg			0,01025	0,00102	Beta
Adverse Event Probability Cataract	>0.0 - <0.5mg		All	0,00517	0,00052	Beta
	0.5 - <2.5mg			0,01205	0,00120	Beta
	2.5 - <5.0mg			0,02341	0,00234	Beta
	5.0 - <7.5mg			0,02582	0,00258	Beta

	7.5 - <15.0mg		0,03184	0,00318	Beta
	≥15.0mg		0,03668	0,00367	Beta
Adverse Event Probability Myocardial Infarction	>0.0 - <0.5mg	All	0,00173	0,00017	Beta
	0.5 - <2.5mg		0,00422	0,00042	Beta
	2.5 - <5.0mg		0,00865	0,00087	Beta
	5.0 - <7.5mg		0,01070	0,00107	Beta
	7.5 - <15.0mg		0,01318	0,00132	Beta
	≥15.0mg		0,01031	0,00103	Beta
Adverse Event Prevalence Heart Failure	>0.0 - <0.5mg	All	0,00173	0,00017	Beta
	0.5 - <2.5mg		0,00577	0,00058	Beta
	2.5 - <5.0mg		0,01263	0,00126	Beta
	5.0 - <7.5mg		0,02004	0,00200	Beta
	7.5 - <15.0mg		0,02139	0,00214	Beta
	≥15.0mg		0,03409	0,00341	Beta
Adverse Event Probability Cerebrovascular Accident	>0.0 - <0.5mg	All	0,00234	0,00023	Beta
	0.5 - <2.5mg		0,00606	0,00061	Beta
	2.5 - <5.0mg		0,00844	0,00084	Beta
	5.0 - <7.5mg		0,01024	0,00102	Beta
	7.5 - <15.0mg		0,00753	0,00075	Beta
	≥15.0mg		0,00619	0,00062	Beta
Adverse Event Prevalence Renal Impairment	>0.0 - <0.5mg	All	0,01060	0,00106	Beta
	0.5 - <2.5mg		0,02730	0,00273	Beta
	2.5 - <5.0mg		0,04402	0,00440	Beta
	5.0 - <7.5mg		0,04819	0,00482	Beta
	7.5 - <15.0mg		0,07215	0,00721	Beta
	≥15.0mg		0,10807	0,01081	Beta
Adverse Event Probability Peptic Ulcer	>0.0 - <0.5mg	All	0,00052	0,00005	Beta
	0.5 - <2.5mg		0,00177	0,00018	Beta

	2.5 - <5.0mg		0,00187	0,00019	Beta
	5.0 - <7.5mg		0,00215	0,00021	Beta
	7.5 - <15.0mg		0,00289	0,00029	Beta
	≥15.0mg		0,01061	0,00106	Beta
Adverse Event Probability Pneumonia	>0.0 - <0.5mg	All	0,00275	0,00027	Beta
	0.5 - <2.5mg		0,00823	0,00082	Beta
	2.5 - <5.0mg		0,01611	0,00161	Beta
	5.0 - <7.5mg		0,01965	0,00197	Beta
	7.5 - <15.0mg		0,02954	0,00295	Beta
	≥15.0mg		0,04614	0,00461	Beta

Discontinuation

Parameter Group	Parameter	Arm	Mean	SE	Distribution
Natural Discontinuation Rate	With OCS	Tezepelumab	0,01300	0,37800	Log-Normal
	Without OCS	Tezepelumab	0,00650	0,16670	Log-Normal
Biologic Response Timing	Response Week	Tezepelumab	52	0,52	Normal
Biologic Response Probability of Discontinuation	With OCS	Tezepelumab	0,08333	0,01881	Beta
	Without OCS	Tezepelumab	0,08333	0,01881	Beta

Costs

Parameter Group	Parameter	Arm	Mean	SE	Distribution
Drug Acquisition	Treatment	Tezepelumab	8 890,90 kr.	889,09 kr.	Gamma
		SoC	265,88 kr.	26,59 kr.	Gamma
	OCS (Per 1mg)	All	0,14 kr	0,01 kr	Gamma
Drug Administration	Doses (Year 1)	Tezepelumab	13,0	0,0	Normal
		SoC	13,0	0,0	Normal
	Doses (Subsequent Years)	Tezepelumab	13,0	0,0	Normal
		SoC	13,0	0,0	Normal

	Minutes Per Dose	Tezepelumab	0,0	0,0	Normal
		SoC	0,0	0,0	Normal
Resource Use Controlled Asthma	GP Visit (Outpatient) (Per Week)	All	0,03100	0,00310	Gamma
	Transportation to hospital		0,03100	0,00310	Gamma
	GP Visit (Home) (Per Week)		0,00082	0,00008	Gamma
	Nurse Visit (Outpatient) (Per Week)		0,05000	0,00500	Gamma
	Transportation to hospital		0,05000	0,00500	Gamma
	Nurse Visit (Home) (Per Week)		0,00000	0,00000	Gamma
	Respiratory Specialist Visit (Outpatient) (Per Week)		0,01600	0,00160	Gamma
	Transportation to hospital		0,01600	0,00160	Gamma
	Spirometry (Per Week)		0,02600	0,00260	Gamma
Resource Use Uncontrolled Asthma	GP Visit (Outpatient) (Per Week)	All	0,14000	0,01400	Gamma
	Transportation to hospital		0,14000	0,01400	Gamma
	GP Visit (Home) (Per Week)		0,02500	0,00250	Gamma
	Nurse Visit (Outpatient) (Per Week)		0,16000	0,01600	Gamma
	Transportation to hospital		0,16000	0,01600	Gamma
	Nurse Visit (Home) (Per Week)		0,00072	0,00007	Gamma
	Respiratory Specialist Visit (Outpatient) (Per Week)		0,09400	0,00940	Gamma
	Transportation to hospital		0,09400	0,00940	Gamma
	Spirometry (Per Week)		0,04900	0,00490	Gamma
Resource Use Exacerbation (OCS Burst)	GP Visit (Outpatient) (Per Week)	All	1,37000	0,13700	Gamma
	Transportation to hospital		1,37000	0,13700	Gamma
	GP Visit (Home) (Per Week)		0,22000	0,02200	Gamma
	Nurse Visit (Outpatient) (Per Week)		0,90000	0,09000	Gamma
	Transportation to hospital		0,90000	0,09000	Gamma
	Nurse Visit (Home) (Per Week)		0,00330	0,00033	Gamma
	Respiratory Specialist Visit (Outpatient) (Per Week)		0,34000	0,03400	Gamma

	Transportation to hospital		0,34000	0,03400	Gamma
	Spirometry (Per Week)		0,29000	0,02900	Gamma
Resource Use Exacerbation (A&E Visit)	GP Visit (Outpatient) (Per Week)	All	1,37000	0,13700	Gamma
	Transportation to hospital		1,37000	0,13700	Gamma
	GP Visit (Home) (Per Week)		0,22000	0,02200	Gamma
	Nurse Visit (Outpatient) (Per Week)		0,90000	0,09000	Gamma
	Transportation to hospital		0,90000	0,09000	Gamma
	Nurse Visit (Home) (Per Week)		0,00330	0,00033	Gamma
	Respiratory Specialist Visit (Outpatient) (Per Week)		0,34000	0,03400	Gamma
	Transportation to hospital		0,34000	0,03400	Gamma
	Spirometry (Per Week)		0,29000	0,02900	Gamma
Resource Use Exacerbation (Hospitalisation)	GP Visit (Outpatient) (Per Week)	All	0,59000	0,05900	Gamma
	Transportation to hospital		0,59000	0,05900	Gamma
	GP Visit (Home) (Per Week)		0,10200	0,01020	Gamma
	Nurse Visit (Outpatient) (Per Week)		1,38000	0,13800	Gamma
	Transportation to hospital		1,38000	0,13800	Gamma
	Nurse Visit (Home) (Per Week)		0,00470	0,00047	Gamma
	Respiratory Specialist Visit (Outpatient) (Per Week)		1,76000	0,17600	Gamma
	Transportation to hospital		1,76000	0,17600	Gamma
	Spirometry (Per Week)		0,46000	0,04600	Gamma
Unit Costs	GP Visit (Outpatient)	All	148,35 kr.	14,84 kr.	Gamma
	Transportation to hospital		231,39 kr.	23,14 kr.	Gamma
	GP Visit (Home)		791,16 kr.	79,12 kr.	Gamma
	Nurse Visit (Outpatient)		550,00 kr.	55,00 kr.	Gamma
	Transportation to hospital		231,39 kr.	23,14 kr.	Gamma
	Nurse Visit (Home)		550,00 kr.	55,00 kr.	Gamma
	Respiratory Specialist Visit (Outpatient)		2 180,00 kr.	218,00 kr.	Gamma

	Transportation to hospital		231,39 kr.	23,14 kr.	Gamma
	Spirometry		124,26 kr.	12,43 kr.	Gamma
	Administration cost per dose		194,65 kr.	19,47 kr.	Gamma
	A&E Visit		2 180,00 kr.	218,00 kr.	Gamma
	Hospitalisation		23 486,00 kr.	2 348,60 kr.	Gamma
Adverse Event Type-2 Diabetes Mellitus	>0.0 - <0.5mg	All	799,26 kr.	79,93 kr.	Gamma
	0.5 - <2.5mg		843,12 kr.	84,31 kr.	Gamma
	2.5 - <5.0mg		843,57 kr.	84,36 kr.	Gamma
	5.0 - <7.5mg		1 337,88 kr.	133,79 kr.	Gamma
	7.5 - <15.0mg		957,82 kr.	95,78 kr.	Gamma
	≥15.0mg		3 285,85 kr.	328,59 kr.	Gamma
Adverse Event Osteoporosis	>0.0 - <0.5mg	All	837,34 kr.	83,73 kr.	Gamma
	0.5 - <2.5mg		1 118,72 kr.	111,87 kr.	Gamma
	2.5 - <5.0mg		2 180,65 kr.	218,06 kr.	Gamma
	5.0 - <7.5mg		2 708,48 kr.	270,85 kr.	Gamma
	7.5 - <15.0mg		2 939,70 kr.	293,97 kr.	Gamma
	≥15.0mg		4 413,87 kr.	441,39 kr.	Gamma
Adverse Event Glaucoma	>0.0 - <0.5mg	All	380,90 kr.	38,09 kr.	Gamma
	0.5 - <2.5mg		428,02 kr.	42,80 kr.	Gamma
	2.5 - <5.0mg		441,55 kr.	44,15 kr.	Gamma
	5.0 - <7.5mg		921,70 kr.	92,17 kr.	Gamma
	7.5 - <15.0mg		550,41 kr.	55,04 kr.	Gamma
	≥15.0mg		808,51 kr.	80,85 kr.	Gamma
Adverse Event Cataract	>0.0 - <0.5mg	All	533,66 kr.	53,37 kr.	Gamma
	0.5 - <2.5mg		600,09 kr.	60,01 kr.	Gamma
	2.5 - <5.0mg		810,59 kr.	81,06 kr.	Gamma
	5.0 - <7.5mg		912,12 kr.	91,21 kr.	Gamma
	7.5 - <15.0mg		680,69 kr.	68,07 kr.	Gamma

	≥15.0mg		671,23 kr.	67,12 kr.	Gamma
Adverse Event Myocardial Infarction	>0.0 - <0.5mg	All	2 877,38 kr.	287,74 kr.	Gamma
	0.5 - <2.5mg		3 132,42 kr.	313,24 kr.	Gamma
	2.5 - <5.0mg		3 322,19 kr.	332,22 kr.	Gamma
	5.0 - <7.5mg		4 378,18 kr.	437,82 kr.	Gamma
	7.5 - <15.0mg		3 400,96 kr.	340,10 kr.	Gamma
	≥15.0mg		5 586,96 kr.	558,70 kr.	Gamma
Adverse Event Heart Failure	>0.0 - <0.5mg	All	2 856,46 kr.	285,65 kr.	Gamma
	0.5 - <2.5mg		3 260,35 kr.	326,04 kr.	Gamma
	2.5 - <5.0mg		3 663,29 kr.	366,33 kr.	Gamma
	5.0 - <7.5mg		4 871,76 kr.	487,18 kr.	Gamma
	7.5 - <15.0mg		3 644,19 kr.	364,42 kr.	Gamma
	≥15.0mg		4 757,71 kr.	475,77 kr.	Gamma
Adverse Event Cerebrovascular Accident	>0.0 - <0.5mg	All	3 174,49 kr.	317,45 kr.	Gamma
	0.5 - <2.5mg		3 598,78 kr.	359,88 kr.	Gamma
	2.5 - <5.0mg		4 125,24 kr.	412,52 kr.	Gamma
	5.0 - <7.5mg		5 124,79 kr.	512,48 kr.	Gamma
	7.5 - <15.0mg		4 027,70 kr.	402,77 kr.	Gamma
	≥15.0mg		5 409,39 kr.	540,94 kr.	Gamma
Adverse Event Renal Impairment	>0.0 - <0.5mg	All	3 394,83 kr.	339,48 kr.	Gamma
	0.5 - <2.5mg		3 900,99 kr.	390,10 kr.	Gamma
	2.5 - <5.0mg		4 348,79 kr.	434,88 kr.	Gamma
	5.0 - <7.5mg		5 047,81 kr.	504,78 kr.	Gamma
	7.5 - <15.0mg		4 490,32 kr.	449,03 kr.	Gamma
	≥15.0mg		6 499,90 kr.	649,99 kr.	Gamma
Adverse Event Peptic Ulcer	>0.0 - <0.5mg	All	2 036,16 kr.	203,62 kr.	Gamma
	0.5 - <2.5mg		2 477,40 kr.	247,74 kr.	Gamma
	2.5 - <5.0mg		2 806,56 kr.	280,66 kr.	Gamma

	5.0 - <7.5mg		3 647,96 kr.	364,80 kr.	Gamma
	7.5 - <15.0mg		2 926,40 kr.	292,64 kr.	Gamma
	≥15.0mg		5 529,56 kr.	552,96 kr.	Gamma
Adverse Event Pneumonia	>0.0 - <0.5mg	All	2 374,03 kr.	237,40 kr.	Gamma
	0.5 - <2.5mg		5 559,71 kr.	555,97 kr.	Gamma
	2.5 - <5.0mg		4 425,30 kr.	442,53 kr.	Gamma
	5.0 - <7.5mg		4 368,67 kr.	436,87 kr.	Gamma
	7.5 - <15.0mg		4 691,69 kr.	469,17 kr.	Gamma
	≥15.0mg		6 781,78 kr.	678,18 kr.	Gamma

Utilities

Parameter Group	Parameter	Arm	Mean	SE	Distribution
Health State	Controlled Asthma	All	0,930	0,001	Beta
	Uncontrolled Asthma		0,769	0,003	Beta
	Controlled Exacerbation (OCS Burst)		0,100	0,010	Beta
	Controlled Exacerbation (A&E Visit)		0,100	0,010	Beta
	Controlled Exacerbation (Hospitalisation)		0,200	0,020	Beta
	Uncontrolled Exacerbation (OCS Burst)		0,100	0,010	Beta
	Uncontrolled Exacerbation (A&E Visit)		0,100	0,010	Beta
	Uncontrolled Exacerbation (Hospitalisation)		0,200	0,020	Beta
Adverse Events	Type-2 Diabetes Mellitus	All	0,062	0,004	Beta
	Osteoporosis		0,042	0,006	Beta
	Glaucoma		0,028	0,006	Beta
	Cataract		0,027	0,006	Beta
	Myocardial Infarction		0,056	0,011	Beta
	Heart Failure		0,103	0,016	Beta
	Cerebrovascular Accident		0,101	0,012	Beta
	Renal Impairment		0,096	0,012	Beta

Peptic Ulcer	0,055	0,014	Beta
Pneumonia	0,079	0,042	Beta

Table 106. Parameters in the probabilistic sensitivity analysis for the T2 low population with 3+ AAER

Baseline Characteristics

Parameter Group	Parameter	Arm	Mean	SE	Distribution
Demographics	Age (Years)	All	51,32	1,03	Normal
	Proportion Male		0,376	0,037	Beta

Transition Probabilities

Parameter Group	Parameter	Arm	Mean	SE	Distribution
Tezepelumab Pre-Assessment With OCS	Controlled Asthma -> Uncontrolled Asthma	Tezepelumab	0,09375	0,03644	Beta
	Controlled Asthma -> Controlled Exacerbation		0,09375	0,03644	Beta
	Uncontrolled Asthma -> Controlled Asthma		0,14599	0,03017	Beta
	Uncontrolled Asthma -> Uncontrolled Exacerbation		0,15328	0,03078	Beta
	Controlled Exacerbation -> Controlled Asthma		0,66667	0,19245	Beta
	Controlled Exacerbation -> Uncontrolled Asthma		0,33333	0,19245	Beta
	Uncontrolled Exacerbation -> Controlled Asthma		0,03030	0,02984	Beta
	Uncontrolled Exacerbation -> Uncontrolled Asthma		0,51515	0,08700	Beta
Tezepelumab Pre-Assessment Without OCS	Controlled Asthma -> Uncontrolled Asthma	Tezepelumab	0,11783	0,01819	Beta
	Controlled Asthma -> Controlled Exacerbation		0,02866	0,00942	Beta
	Uncontrolled Asthma -> Controlled Asthma		0,16000	0,01778	Beta
	Uncontrolled Asthma -> Uncontrolled Exacerbation		0,10588	0,01493	Beta
	Controlled Exacerbation -> Controlled Asthma		0,57143	0,18704	Beta
	Controlled Exacerbation -> Uncontrolled Asthma		0,28571	0,17075	Beta

	Uncontrolled Exacerbation -> Controlled Asthma		0,09259	0,03945	Beta
	Uncontrolled Exacerbation -> Uncontrolled Asthma		0,72222	0,06095	Beta
Tezepelumab Post-Assessment With OCS	Controlled Asthma -> Uncontrolled Asthma	Tezepelumab	0,09524	0,03698	Beta
	Controlled Asthma -> Controlled Exacerbation		0,12067	0,01207	Beta
	Uncontrolled Asthma -> Controlled Asthma		0,15833	0,03332	Beta
	Uncontrolled Asthma -> Uncontrolled Exacerbation		0,15205	0,01520	Beta
	Controlled Exacerbation -> Controlled Asthma		0,80000	0,17889	Beta
	Controlled Exacerbation -> Uncontrolled Asthma		0,20000	0,17889	Beta
	Uncontrolled Exacerbation -> Controlled Asthma		0,07143	0,06883	Beta
	Uncontrolled Exacerbation -> Uncontrolled Asthma		0,71429	0,12074	Beta
Tezepelumab Post-Assessment Without OCS	Controlled Asthma -> Uncontrolled Asthma	Tezepelumab	0,11921	0,01865	Beta
	Controlled Asthma -> Controlled Exacerbation		0,03524	0,00352	Beta
	Uncontrolled Asthma -> Controlled Asthma		0,16296	0,01835	Beta
	Uncontrolled Asthma -> Uncontrolled Exacerbation		0,13515	0,01352	Beta
	Controlled Exacerbation -> Controlled Asthma		0,60000	0,21909	Beta
	Controlled Exacerbation -> Uncontrolled Asthma		0,40000	0,21909	Beta
	Uncontrolled Exacerbation -> Controlled Asthma		0,13158	0,05484	Beta
	Uncontrolled Exacerbation -> Uncontrolled Asthma		0,81579	0,06289	Beta
SoC With OCS	Controlled Asthma -> Uncontrolled Asthma	SoC	0,08451	0,03301	Beta
	Controlled Asthma -> Controlled Exacerbation		0,09859	0,03538	Beta
	Uncontrolled Asthma -> Controlled Asthma		0,06806	0,01822	Beta
	Uncontrolled Asthma -> Uncontrolled Exacerbation		0,12565	0,02398	Beta
	Controlled Exacerbation -> Controlled Asthma		0,55556	0,16563	Beta
	Controlled Exacerbation -> Uncontrolled Asthma		0,22222	0,13858	Beta
	Uncontrolled Exacerbation -> Controlled Asthma		0,07143	0,04867	Beta
	Uncontrolled Exacerbation -> Uncontrolled Asthma		0,75000	0,08183	Beta
	Controlled Asthma -> Uncontrolled Asthma	SoC	0,13333	0,02434	Beta

SoC Without OCS	Controlled Asthma -> Controlled Exacerbation		0,10769	0,02220	Beta
	Uncontrolled Asthma -> Controlled Asthma		0,13213	0,01856	Beta
	Uncontrolled Asthma -> Uncontrolled Exacerbation		0,17718	0,02092	Beta
	Controlled Exacerbation -> Controlled Asthma		0,66667	0,09623	Beta
	Controlled Exacerbation -> Uncontrolled Asthma		0,04167	0,04079	Beta
	Uncontrolled Exacerbation -> Controlled Asthma		0,10843	0,03413	Beta
	Uncontrolled Exacerbation -> Uncontrolled Asthma		0,54217	0,05469	Beta
SoC With OCS 2nd year and on	Controlled Asthma -> Uncontrolled Asthma	SoC	0,08451	0,03301	Beta
	Controlled Asthma -> Controlled Exacerbation		0,14991	0,01499	Beta
	Uncontrolled Asthma -> Controlled Asthma		0,06806	0,01822	Beta
	Uncontrolled Asthma -> Uncontrolled Exacerbation		0,19105	0,01911	Beta
	Controlled Exacerbation -> Controlled Asthma		0,55556	0,16563	Beta
	Controlled Exacerbation -> Uncontrolled Asthma		0,22222	0,13858	Beta
	Uncontrolled Exacerbation -> Controlled Asthma		0,07143	0,04867	Beta
	Uncontrolled Exacerbation -> Uncontrolled Asthma		0,75000	0,08183	Beta
SoC Without OCS 2nd year and on	Controlled Asthma -> Uncontrolled Asthma	SoC	0,13333	0,02434	Beta
	Controlled Asthma -> Controlled Exacerbation		0,16374	0,01637	Beta
	Uncontrolled Asthma -> Controlled Asthma		0,13213	0,01856	Beta
	Uncontrolled Asthma -> Uncontrolled Exacerbation		0,26939	0,02694	Beta
	Controlled Exacerbation -> Controlled Asthma		0,66667	0,09623	Beta
	Controlled Exacerbation -> Uncontrolled Asthma		0,04167	0,04079	Beta
	Uncontrolled Exacerbation -> Controlled Asthma		0,10843	0,03413	Beta
	Uncontrolled Exacerbation -> Uncontrolled Asthma		0,54217	0,05469	Beta

Exacerbations

Parameter Group	Parameter	Arm	Mean	SE	Distribution
	Proportion OCS Burst	Tezepelumab	0,857	0,132	Beta

Distribution Controlled With OCS		SoC	0,900	0,095	Beta
	Proportion A&E Visit	Tezepelumab	0,000	0,000	Beta
		SoC	0,100	0,095	Beta
	Proportion Hospitalisation	Tezepelumab	0,143	0,132	Beta
		SoC	0,000	0,000	Beta
Distribution Controlled Without OCS	Proportion OCS Burst	Tezepelumab	1,000	0,000	Beta
		SoC	0,938	0,043	Beta
	Proportion A&E Visit	Tezepelumab	0,000	0,000	Beta
		SoC	0,031	0,031	Beta
	Proportion Hospitalisation	Tezepelumab	0,000	0,000	Beta
		SoC	0,031	0,031	Beta
Distribution Uncontrolled With OCS	Proportion OCS Burst	Tezepelumab	0,854	0,055	Beta
		SoC	0,735	0,076	Beta
	Proportion A&E Visit	Tezepelumab	0,073	0,041	Beta
		SoC	0,000	0,000	Beta
	Proportion Hospitalisation	Tezepelumab	0,073	0,041	Beta
		SoC	0,265	0,076	Beta
Distribution Uncontrolled Without OCS	Proportion OCS Burst	Tezepelumab	0,902	0,038	Beta
		SoC	0,833	0,037	Beta
	Proportion A&E Visit	Tezepelumab	0,066	0,032	Beta
		SoC	0,010	0,010	Beta
	Proportion Hospitalisation	Tezepelumab	0,033	0,023	Beta
		SoC	0,157	0,036	Beta
Duration Cost Component Controlled (Weeks)	OCS Burst	Tezepelumab	1,29	0,14	Normal
		SoC	1,27	0,15	Normal
	A&E Visit	Tezepelumab	1,29	0,14	Normal
		SoC	1,27	0,15	Normal
	Hospitalisation	Tezepelumab	1,14	0,14	Normal
		SoC	3,06	1,08	Normal
Duration Cost Component Uncontrolled (Weeks)	OCS Burst	Tezepelumab	1,25	0,07	Normal
		SoC	1,23	0,05	Normal
	A&E Visit	Tezepelumab	1,25	0,07	Normal
		SoC	1,23	0,05	Normal
	Hospitalisation	Tezepelumab	1,64	0,34	Normal
		SoC	2,90	0,58	Normal

Duration Utility Component Controlled (Weeks)	OCS Burst	Tezepelumab	1,29	0,14	Normal
		SoC	1,27	0,15	Normal
	A&E Visit	Tezepelumab	1,29	0,14	Normal
		SoC	1,27	0,15	Normal
	Hospitalisation	Tezepelumab	1,14	0,14	Normal
		SoC	3,06	1,08	Normal
Duration Utility Component Uncontrolled (Weeks)	OCS Burst	Tezepelumab	1,25	0,07	Normal
		SoC	1,23	0,05	Normal
	A&E Visit	Tezepelumab	1,25	0,07	Normal
		SoC	1,23	0,05	Normal
	Hospitalisation	Tezepelumab	1,64	0,34	Normal
		SoC	2,90	0,58	Normal
Mortality Risk OCS Burst	Age 18-44	All	0,00019	0,00003	Beta
	Age 45+		0,00312	0,00024	Beta
Mortality Risk A&E Visit	Age 18-44	All	0,00197	0,00034	Beta
	Age 45+		0,03189	0,00242	Beta
Mortality Risk Hospitalisation	Age 18-24	All	0,03189	0,00319	Beta
	Age 25-34		0,00000	0,00000	Beta
	Age 36-44		0,00058	0,00006	Beta
	Age 45-54		0,00080	0,00008	Beta
	Age 55-64		0,00080	0,00008	Beta
	Age 65+		0,00302	0,00030	Beta

OCS

Parameter Group	Parameter	Arm	Mean	SE	Distribution
Baseline OCS	Proportion on OCS	All	0,195	0,032	Beta
	OCS Dose (mg/Day)		11,05	1,27	Normal
OCS Sparing Timing	Sparing Week	All	52,00	0,00	Normal
OCS Sparing Reduction	Proportion with No Reduction	Tezepelumab	0,286	0,171	Beta
		SoC	0,250	0,125	Beta
	Proportion with >0% - <50%	Tezepelumab	0,143	0,132	Beta
		SoC	0,083	0,080	Beta
	Proportion with 50% - <75%	Tezepelumab	0,000	0,000	Beta
		SoC	0,000	0,000	Beta
	Proportion with 75% - <90%	Tezepelumab	0,000	0,000	Beta

		SoC	0,083	0,080	Beta
	Proportion with 90% - 100% (Discontinuation)	Tezepelumab	0,571	0,187	Beta
		SoC	0,583	0,142	Beta
	Dose Reduction Scaling	All	Medium		
Adverse Event Prevalence Type-2 Diabetes Mellitus	>0.0 - <0.5mg	All	0,00629	0,00063	Beta
	0.5 - <2.5mg		0,01368	0,00137	Beta
	2.5 - <5.0mg		0,02005	0,00200	Beta
	5.0 - <7.5mg		0,02457	0,00246	Beta
	7.5 - <15.0mg		0,04235	0,00423	Beta
	≥15.0mg		0,07950	0,00795	Beta
Adverse Event Prevalence Osteoporosis	>0.0 - <0.5mg	All	0,00200	0,00020	Beta
	0.5 - <2.5mg		0,00660	0,00066	Beta
	2.5 - <5.0mg		0,01531	0,00153	Beta
	5.0 - <7.5mg		0,02043	0,00204	Beta
	7.5 - <15.0mg		0,03319	0,00332	Beta
	≥15.0mg		0,01176	0,00118	Beta
Adverse Event Prevalence Glaucoma	>0.0 - <0.5mg	All	0,00136	0,00014	Beta
	0.5 - <2.5mg		0,00281	0,00028	Beta
	2.5 - <5.0mg		0,00381	0,00038	Beta
	5.0 - <7.5mg		0,00759	0,00076	Beta
	7.5 - <15.0mg		0,00468	0,00047	Beta
	≥15.0mg		0,01025	0,00102	Beta
Adverse Event Probability Cataract	>0.0 - <0.5mg	All	0,00517	0,00052	Beta
	0.5 - <2.5mg		0,01205	0,00120	Beta
	2.5 - <5.0mg		0,02341	0,00234	Beta
	5.0 - <7.5mg		0,02582	0,00258	Beta
	7.5 - <15.0mg		0,03184	0,00318	Beta
	≥15.0mg		0,03668	0,00367	Beta
Adverse Event Probability Myocardial Infarction	>0.0 - <0.5mg	All	0,00173	0,00017	Beta
	0.5 - <2.5mg		0,00422	0,00042	Beta
	2.5 - <5.0mg		0,00865	0,00087	Beta
	5.0 - <7.5mg		0,01070	0,00107	Beta
	7.5 - <15.0mg		0,01318	0,00132	Beta
	≥15.0mg		0,01031	0,00103	Beta
	>0.0 - <0.5mg	All	0,00173	0,00017	Beta

Adverse Event Prevalence Heart Failure	0.5 - <2.5mg		0,00577	0,00058	Beta
	2.5 - <5.0mg		0,01263	0,00126	Beta
	5.0 - <7.5mg		0,02004	0,00200	Beta
	7.5 - <15.0mg		0,02139	0,00214	Beta
	≥15.0mg		0,03409	0,00341	Beta
Adverse Event Probability Cerebrovascular Accident	>0.0 - <0.5mg	All	0,00234	0,00023	Beta
	0.5 - <2.5mg		0,00606	0,00061	Beta
	2.5 - <5.0mg		0,00844	0,00084	Beta
	5.0 - <7.5mg		0,01024	0,00102	Beta
	7.5 - <15.0mg		0,00753	0,00075	Beta
	≥15.0mg		0,00619	0,00062	Beta
Adverse Event Prevalence Renal Impairment	>0.0 - <0.5mg	All	0,01060	0,00106	Beta
	0.5 - <2.5mg		0,02730	0,00273	Beta
	2.5 - <5.0mg		0,04402	0,00440	Beta
	5.0 - <7.5mg		0,04819	0,00482	Beta
	7.5 - <15.0mg		0,07215	0,00721	Beta
	≥15.0mg		0,10807	0,01081	Beta
Adverse Event Probability Peptic Ulcer	>0.0 - <0.5mg	All	0,00052	0,00005	Beta
	0.5 - <2.5mg		0,00177	0,00018	Beta
	2.5 - <5.0mg		0,00187	0,00019	Beta
	5.0 - <7.5mg		0,00215	0,00021	Beta
	7.5 - <15.0mg		0,00289	0,00029	Beta
	≥15.0mg		0,01061	0,00106	Beta
Adverse Event Probability Pneumonia	>0.0 - <0.5mg	All	0,00275	0,00027	Beta
	0.5 - <2.5mg		0,00823	0,00082	Beta
	2.5 - <5.0mg		0,01611	0,00161	Beta
	5.0 - <7.5mg		0,01965	0,00197	Beta
	7.5 - <15.0mg		0,02954	0,00295	Beta
	≥15.0mg		0,04614	0,00461	Beta

Discontinuation

Parameter Group	Parameter	Arm	Mean	SE	Distribution
Natural Discontinuation Rate	With OCS	Tezepelumab	0,01300	0,37800	Log-Normal
	Without OCS	Tezepelumab	0,00650	0,16670	Log-Normal

Biologic Response Timing	Response Week	Tezepelumab	52,00000	0,00	Normal
Biologic Response Probability of Discontinuation	With OCS	Tezepelumab	0,06557	0,03169	Beta
	Without OCS	Tezepelumab	0,06557	0,03169	Beta

Costs

Parameter Group	Parameter	Arm	Mean	SE	Distribution
Drug Acquisition	Treatment	Tezepelumab	8 890,90 kr.	889,09 kr.	Gamma
		SoC	265,88 kr.	26,59 kr.	Gamma
	OCS (Per 1mg)	All	0,14 kr	0,01 kr	Gamma
Drug Administration	Doses (Year 1)	Tezepelumab	13,0	0,0	Normal
		SoC	13,0	0,0	Normal
	Doses (Subsequent Years)	Tezepelumab	13,0	0,0	Normal
		SoC	13,0	0,0	Normal
	Minutes Per Dose	Tezepelumab	0,0	0,0	Normal
		SoC	0,0	0,0	Normal
Resource Use Controlled Asthma	GP Visit (Outpatient) (Per Week)	All	0,03100	0,00310	Gamma
	Transportation to hospital		0,03100	0,00310	Gamma
	GP Visit (Home) (Per Week)		0,00082	0,00008	Gamma
	Nurse Visit (Outpatient) (Per Week)		0,05000	0,00500	Gamma
	Transportation to hospital		0,05000	0,00500	Gamma
	Nurse Visit (Home) (Per Week)		0,00000	0,00000	Gamma
	Respiratory Specialist Visit (Outpatient) (Per Week)		0,01600	0,00160	Gamma
	Transportation to hospital		0,01600	0,00160	Gamma
	Spirometry (Per Week)		0,02600	0,00260	Gamma
Resource Use Uncontrolled Asthma	GP Visit (Outpatient) (Per Week)	All	0,14000	0,01400	Gamma
	Transportation to hospital		0,14000	0,01400	Gamma
	GP Visit (Home) (Per Week)		0,02500	0,00250	Gamma
	Nurse Visit (Outpatient) (Per Week)		0,16000	0,01600	Gamma
	Transportation to hospital		0,16000	0,01600	Gamma
	Nurse Visit (Home) (Per Week)		0,00072	0,00007	Gamma
	Respiratory Specialist Visit (Outpatient) (Per Week)		0,09400	0,00940	Gamma
	Transportation to hospital		0,09400	0,00940	Gamma
	Spirometry (Per Week)		0,04900	0,00490	Gamma

Resource Use Exacerbation (OCS Burst)	GP Visit (Outpatient) (Per Week)	All	1,37000	0,13700	Gamma
	Transportation to hospital		1,37000	0,13700	Gamma
	GP Visit (Home) (Per Week)		0,22000	0,02200	Gamma
	Nurse Visit (Outpatient) (Per Week)		0,90000	0,09000	Gamma
	Transportation to hospital		0,90000	0,09000	Gamma
	Nurse Visit (Home) (Per Week)		0,00330	0,00033	Gamma
	Respiratory Specialist Visit (Outpatient) (Per Week)		0,34000	0,03400	Gamma
	Transportation to hospital		0,34000	0,03400	Gamma
	Spirometry (Per Week)		0,29000	0,02900	Gamma
Resource Use Exacerbation (A&E Visit)	GP Visit (Outpatient) (Per Week)	All	1,37000	0,13700	Gamma
	Transportation to hospital		1,37000	0,13700	Gamma
	GP Visit (Home) (Per Week)		0,22000	0,02200	Gamma
	Nurse Visit (Outpatient) (Per Week)		0,90000	0,09000	Gamma
	Transportation to hospital		0,90000	0,09000	Gamma
	Nurse Visit (Home) (Per Week)		0,00330	0,00033	Gamma
	Respiratory Specialist Visit (Outpatient) (Per Week)		0,34000	0,03400	Gamma
	Transportation to hospital		0,34000	0,03400	Gamma
	Spirometry (Per Week)		0,29000	0,02900	Gamma
Resource Use Exacerbation (Hospitalisation)	GP Visit (Outpatient) (Per Week)	All	0,59000	0,05900	Gamma
	Transportation to hospital		0,59000	0,05900	Gamma
	GP Visit (Home) (Per Week)		0,10200	0,01020	Gamma
	Nurse Visit (Outpatient) (Per Week)		1,38000	0,13800	Gamma
	Transportation to hospital		1,38000	0,13800	Gamma
	Nurse Visit (Home) (Per Week)		0,00470	0,00047	Gamma
	Respiratory Specialist Visit (Outpatient) (Per Week)		1,76000	0,17600	Gamma
	Transportation to hospital		1,76000	0,17600	Gamma
	Spirometry (Per Week)		0,46000	0,04600	Gamma
Unit Costs	GP Visit (Outpatient)	All	148,35 kr.	14,84 kr.	Gamma
	Transportation to hospital		231,39 kr.	23,14 kr.	Gamma
	GP Visit (Home)		791,16 kr.	79,12 kr.	Gamma
	Nurse Visit (Outpatient)		550,00 kr.	55,00 kr.	Gamma
	Transportation to hospital		231,39 kr.	23,14 kr.	Gamma
	Nurse Visit (Home)		550,00 kr.	55,00 kr.	Gamma
	Respiratory Specialist Visit (Outpatient)		2 180,00 kr.	218,00 kr.	Gamma

	Transportation to hospital		231,39 kr.	23,14 kr.	Gamma
	Spirometry		124,26 kr.	12,43 kr.	Gamma
	Administration cost per dose		194,65 kr.	19,47 kr.	Gamma
	A&E Visit		2 180,00 kr.	218,00 kr.	Gamma
	Hospitalisation		23 486,00 kr.	2 348,60 kr.	Gamma
Adverse Event Type-2 Diabetes Mellitus	>0.0 - <0.5mg	All	799,26 kr.	79,93 kr.	Gamma
	0.5 - <2.5mg		843,12 kr.	84,31 kr.	Gamma
	2.5 - <5.0mg		843,57 kr.	84,36 kr.	Gamma
	5.0 - <7.5mg		1 337,88 kr.	133,79 kr.	Gamma
	7.5 - <15.0mg		957,82 kr.	95,78 kr.	Gamma
	≥15.0mg		3 285,85 kr.	328,59 kr.	Gamma
Adverse Event Osteoporosis	>0.0 - <0.5mg	All	837,34 kr.	83,73 kr.	Gamma
	0.5 - <2.5mg		1 118,72 kr.	111,87 kr.	Gamma
	2.5 - <5.0mg		2 180,65 kr.	218,06 kr.	Gamma
	5.0 - <7.5mg		2 708,48 kr.	270,85 kr.	Gamma
	7.5 - <15.0mg		2 939,70 kr.	293,97 kr.	Gamma
	≥15.0mg		4 413,87 kr.	441,39 kr.	Gamma
Adverse Event Glaucoma	>0.0 - <0.5mg	All	380,90 kr.	38,09 kr.	Gamma
	0.5 - <2.5mg		428,02 kr.	42,80 kr.	Gamma
	2.5 - <5.0mg		441,55 kr.	44,15 kr.	Gamma
	5.0 - <7.5mg		921,70 kr.	92,17 kr.	Gamma
	7.5 - <15.0mg		550,41 kr.	55,04 kr.	Gamma
	≥15.0mg		808,51 kr.	80,85 kr.	Gamma
Adverse Event Cataract	>0.0 - <0.5mg	All	533,66 kr.	53,37 kr.	Gamma
	0.5 - <2.5mg		600,09 kr.	60,01 kr.	Gamma
	2.5 - <5.0mg		810,59 kr.	81,06 kr.	Gamma
	5.0 - <7.5mg		912,12 kr.	91,21 kr.	Gamma
	7.5 - <15.0mg		680,69 kr.	68,07 kr.	Gamma
	≥15.0mg		671,23 kr.	67,12 kr.	Gamma
Adverse Event Myocardial Infarction	>0.0 - <0.5mg	All	2 877,38 kr.	287,74 kr.	Gamma
	0.5 - <2.5mg		3 132,42 kr.	313,24 kr.	Gamma
	2.5 - <5.0mg		3 322,19 kr.	332,22 kr.	Gamma
	5.0 - <7.5mg		4 378,18 kr.	437,82 kr.	Gamma
	7.5 - <15.0mg		3 400,96 kr.	340,10 kr.	Gamma
	≥15.0mg		5 586,96 kr.	558,70 kr.	Gamma

Adverse Event Heart Failure	>0.0 - <0.5mg	All	2 856,46 kr.	285,65 kr.	Gamma
	0.5 - <2.5mg		3 260,35 kr.	326,04 kr.	Gamma
	2.5 - <5.0mg		3 663,29 kr.	366,33 kr.	Gamma
	5.0 - <7.5mg		4 871,76 kr.	487,18 kr.	Gamma
	7.5 - <15.0mg		3 644,19 kr.	364,42 kr.	Gamma
	≥15.0mg		4 757,71 kr.	475,77 kr.	Gamma
Adverse Event Cerebrovascular Accident	>0.0 - <0.5mg	All	3 174,49 kr.	317,45 kr.	Gamma
	0.5 - <2.5mg		3 598,78 kr.	359,88 kr.	Gamma
	2.5 - <5.0mg		4 125,24 kr.	412,52 kr.	Gamma
	5.0 - <7.5mg		5 124,79 kr.	512,48 kr.	Gamma
	7.5 - <15.0mg		4 027,70 kr.	402,77 kr.	Gamma
	≥15.0mg		5 409,39 kr.	540,94 kr.	Gamma
Adverse Event Renal Impairment	>0.0 - <0.5mg	All	3 394,83 kr.	339,48 kr.	Gamma
	0.5 - <2.5mg		3 900,99 kr.	390,10 kr.	Gamma
	2.5 - <5.0mg		4 348,79 kr.	434,88 kr.	Gamma
	5.0 - <7.5mg		5 047,81 kr.	504,78 kr.	Gamma
	7.5 - <15.0mg		4 490,32 kr.	449,03 kr.	Gamma
	≥15.0mg		6 499,90 kr.	649,99 kr.	Gamma
Adverse Event Peptic Ulcer	>0.0 - <0.5mg	All	2 036,16 kr.	203,62 kr.	Gamma
	0.5 - <2.5mg		2 477,40 kr.	247,74 kr.	Gamma
	2.5 - <5.0mg		2 806,56 kr.	280,66 kr.	Gamma
	5.0 - <7.5mg		3 647,96 kr.	364,80 kr.	Gamma
	7.5 - <15.0mg		2 926,40 kr.	292,64 kr.	Gamma
	≥15.0mg		5 529,56 kr.	552,96 kr.	Gamma
Adverse Event Pneumonia	>0.0 - <0.5mg	All	2 374,03 kr.	237,40 kr.	Gamma
	0.5 - <2.5mg		5 559,71 kr.	555,97 kr.	Gamma
	2.5 - <5.0mg		4 425,30 kr.	442,53 kr.	Gamma
	5.0 - <7.5mg		4 368,67 kr.	436,87 kr.	Gamma
	7.5 - <15.0mg		4 691,69 kr.	469,17 kr.	Gamma
	≥15.0mg		6 781,78 kr.	678,18 kr.	Gamma

Utilities

Parameter Group	Parameter	Arm	Mean	SE	Distribution
Health State	Controlled Asthma	All	0,930	0,001	Beta
	Uncontrolled Asthma		0,769	0,003	Beta

	Controlled Exacerbation (OCS Burst)		0,100	0,010	Beta
	Controlled Exacerbation (A&E Visit)		0,100	0,010	Beta
	Controlled Exacerbation (Hospitalisation)		0,200	0,020	Beta
	Uncontrolled Exacerbation (OCS Burst)		0,100	0,010	Beta
	Uncontrolled Exacerbation (A&E Visit)		0,100	0,010	Beta
	Uncontrolled Exacerbation (Hospitalisation)		0,200	0,020	Beta
Adverse Events	Type-2 Diabetes Mellitus	All	0,062	0,004	Beta
	Osteoporosis		0,042	0,006	Beta
	Glaucoma		0,028	0,006	Beta
	Cataract		0,027	0,006	Beta
	Myocardial Infarction		0,056	0,011	Beta
	Heart Failure		0,103	0,016	Beta
	Cerebrovascular Accident		0,101	0,012	Beta
	Renal Impairment		0,096	0,012	Beta
	Peptic Ulcer		0,055	0,014	Beta
	Pneumonia		0,079	0,042	Beta

Appendices K Patient characteristics of the high dose ICS population (Company-specific appendices)

Characteristic	Teze 210 mg Q4W (N=397)	Placebo (N=398)	Total (N=795)
High dose inhaled glucocorticoids – no. (%)	397 (100,0)	398 (100,0)	795 (100,0)
Age – Yr (mean)	51,4	49,3	50,3
Male sex – no. (%)	143 (36,0)	149 (37,4)	292 (36,7)
White race – no. (%)	252 (63,5)	254 (63,8)	506 (63,6)
Body-mass index (median)	27,80	27,40	27,70
Use of oral glucocorticoids – no. (%)			
Yes	47 (11,8)	42 (10,6)	89 (11,2)
No	350 (88,2)	356 (89,4)	706 (88,8)
PEF post-bronchodilator (L/min)	326,0	328, 0	326,0
FeNO level			
No. of patients evaluated	393	394	787
Mean – ppb	42,88	47,77	45,33
Median – ppb	32,00	31,00	32,00
<25 ppb – no. (%)	158 (40,2)	154 (39,1)	312 (39,6)
≥ ppb – no. (%)	235 (59,8)	240 (60,9)	475 (60,4)
Blood eosinophil count			
Mean – cells/µl	333,17 ± 265,53	383,24 ± 548,60	358,24 ± 431,59
Median - cells/µl	250,00	280,00	270,00
<150 cells/µl – no. (%)	96 (24,2)	93 (23,4)	189 (23,8)
<300 cells/µl – no. (%)	226 (56,9)	217 (54,5)	443 (55,7)
≥300 cells/µl – no. (%)	171 (43,1)	181 (45,5)	352 (44,3)
Serum total IgE – IU/ml			
Mean	497,81 ± 821,03	629,00 ± 1220,90	563,48 ± 1042,02
Median	198,30	189,80	194,20
Any perennial FEIA positive – no. (%)	255 (64,2)	258 (64,8)	513 (64,5)

***Source**: AstraZeneca/Amgen Data on File (NAVIGATOR)*

16.

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