Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende dupilumab til behandling af svær atopisk eksem hos børn fra 6 mdr. til 5 år

Vers. 1.0

Bilagsoversigt

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

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05.06.2023

DBS/INK

Prisnotat

Dato for behandling i Medicinrådet	Juni 2023
Leverandør	Sanofi-Aventis
Lægemiddel	Dupixent (dupilumab)
Ansøgt indikation	Dupixent (dupilumab) til behandling af svær atopisk eksem hos børn fra 6 mdr. til 5 år
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende pris på Dupixent:

Tabel 1: Aftalepris

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP, (DKK)	Rabatprocent ift. AIP
Dupixent	200 mg	Sprøjte	7.989,84	[redacted]	[redacted]
Dupixent	300 mg	sprøjte	8.460,47	[redacted]	[redacted]

Aftaleforhold

[redacted]

Dupixent indgår i behandlingsvejledninger indenfor behandling af svær astma, atopisk eksem og svær rhinosinuitis med næsepolypper

Konkurrencesituationen

Dupixent er den eneste systemiske behandling til denne population (børn op til 6 år) med svær atopisk eksem.

Tabel 2: Sammenligning af lægemiddeludgifter

Læge-middel	Styrke	Paknings størrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Doseringer over 24 md.	Lægemiddeludgift pr. 24 md (SAIP, DKK)
Dupixent	200 mg	2 stk.	< 15 kg initial 200 mg SC som enkeltdosis efterfuldt af 200 mg hver 4. uge	[redacted]	26,09	[redacted]
Dupixent	300 mg	2 stk.	15-30 kg initial 300 mg SC som enkeltdosis efterfuldt af 300 mg hver 4. uge	[redacted]	26,09	[redacted]

Status fra andre lande

Land	Status	Link
Norge	Under vurdering	status link

Konklusion

[redacted]

Application for the assessment of dupilumab for children (6 months to <6 years) with severe atopic dermatitis

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Colour scheme for text highlighting	
Colour of highlighted text	**Definition of highlighted text**
	Confidential information

1. Basic information

Contact information	
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Overview of the pharmaceutical	
Proprietary name	Dupixent
Generic name	Dupilumab
Marketing authorization holder in Denmark	Sanofi A/S
ATC code	D11AH05
Pharmacotherapeutic group	Other dermatological preparations, agents for dermatitis, excluding corticosteroids
Active substance(s)	Dupilumab
Pharmaceutical form(s)	Solution for injection
Mechanism of action	Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits interleukin (IL)-4 and IL-13 signalling. Dupilumab inhibits IL-4 signalling via the Type I receptor (IL-4Rα/γc), and both IL-4 and IL-13 signalling through the Type II receptor (IL-4Rα/IL-13Rα). IL-4 and IL-13 are major drivers of human type 2 inflammatory disease, such as atopic dermatitis (AD). Blocking the IL-4/IL-13 pathway with dupilumab in patients decreases many of the mediators of type 2 inflammation (1).
Dosage regimen	Dupilumab is dosed based on patients' weight: • ≥5 to <15 kg: 200 mg dupilumab every 4 weeks with no loading dose • ≥15 to <30 kg: 300 mg dupilumab every 4 weeks with no loading dose

Overview of the pharmaceutical	
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Dupilumab is indicated as treatment of children (6 months to <6 years) with severe AD who are candidates for systemic therapy.
Other approved therapeutic indications	**Atopic dermatitis** Adults and adolescents Dupilumab is indicated for the treatment of moderate-to-severe AD in adults and adolescents 12 years and older who are candidates for systemic therapy. Children 6 to 11 years of age Dupilumab is indicated for the treatment of severe AD in children 6 to 11 years old who are candidates for systemic therapy. **Asthma** Adults and adolescents Dupilumab 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 fraction of exhaled nitric oxide (FeNO) who are inadequately controlled with high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment. Children 6 to 11 years of age Dupilumab is indicated in children 6 to 11 years old as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled FeNO who are inadequately controlled with medium- to high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment. **Chronic rhinosinusitis with nasal polyposis** Dupilumab is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe chronic rhinosinusitis with nasal polyposis for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control. **Prurigo Nodularis (PN)** Dupilumab is indicated for the treatment of adults with moderate-to-severe prurigo nodularis who are candidates for systemic therapy. **Eosinophilic esophagitis (EoE)** Dupilumab is indicated for the treatment of eosinophilic esophagitis in adults and adolescents 12 years and older, weighing at least 40 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy.
Will dispensing be restricted to hospitals?	Yes

Overview of the pharmaceutical	
Combination therapy and/or co-medication	Dupilumab can be used with or without topical corticosteroids (TCS). Topical calcineurin inhibitors (TCI) may be used, but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas.
Packaging – types, sizes/number of units, and concentrations	Dupilumab is available as: • 2 x 200 mg pre-filled syringes • 2 x 200 mg pre-filled pens • 2 x 300 mg pre-filled syringes • 2 x 300 mg pre-filled pen It should be noted that the pre-filled pens are not intended for use in children below the age of 12.
Orphan drug designation	No

2. Abbreviations

AD	Atopic dermatitis
AE	Adverse event
ALSPAC	Avon Longitudinal Study of Parents and Children
BSA	Body surface area
CDLQI	Children's Dermatology Life Quality Index
CMH	Cochran-Mantel-Haenszel
CI	Confidence intervals
CSR	Clinical study report
DALYs	Disability-adjusted life years
DARC	The Danish Allergy Research Centre
DDS	The Danish Society of Dermatology
DMC	Danish Medicines Council
DSA	Deterministic sensitivity analysis
EASI	Eczema Area and Severity Index
EMA	The European Medicines Agency
EPI-CARE	Epidemiology of Children with Atopic Dermatitis Reporting on their Experience
ETFAD	European Task Force on Atopic Dermatitis
FAS	Full analysis set
FeNO	Nitric oxide
GP	General practitioner
HLT	High Level Term
HOME	Harmonising Outcome Measures for Eczema
HRQoL	Health-related quality of life
IDQOL	Infants' Dermatitis Quality of Life Index
IGA	Investigators Global Assessment
IL	Interleukin
LS	Least square
MI	Multiple imputation
NEC	Necrotising enterocolitis
NRS	Numerical rating scale
POEM	The Patient-Oriented Eczema Measure
PPP	Pharmacy purchasing price
PT	Preferred Term
QoL	Quality of life
RR	Risk ratio
SAE	Serious adverse event
SAF	Safety analysis set
SCORAD	Scoring Atopic Dermatitis
SD	Standard deviation
SE	Standard error
SOC	System Organ Class
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
TEAE	Treatment-emergent adverse events
Th0	Type 0 helper T cells

Th2	Type 2 helper T cells
WOCF	Worst-observation-carried-forward

3. Tables and Figures

4. Summary

AD is a chronic type 2 immune-mediated inflammatory skin disease (2–5). The onset of AD typically begins in early infancy or childhood (around 60% of cases begin by 12 months of age) and can persist into adulthood in severe cases (4–8). AD is frequently the first step of the 'atopic march', where underlying type 2 inflammation leads to the development of further allergic disorders during infancy and childhood (3,5,9). AD is associated with a substantial humanistic burden and has major implications on the quality of life (QoL) for both infants and children with AD and their caregivers and families. The intense pruritis leads to sleep disturbances and emotional stress, which impairs QoL substantially among infants with AD and their caregivers (3,10–16). The burden of disease means that AD patients have lower chances of achieving various levels of educational attainment, from primary school to higher education (17). Furthermore, the association of AD with ADHD has been shown by several studies. A German study on children's mental health problems involving 2,916 infants found an association between AD and ADHD (18). The study found that infants with AD are at increased risk of mental health problems at age 10. Even if cleared afterwards, eczema at age 1 to 2 years may cause persistent emotional and behavioural difficulties (18).

Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits IL-4 and IL-13 signalling, and it is the only fully human monoclonal antibody that inhibits both IL-4 and IL-13 signalling, which are the key central drivers of AD and other type 2 inflammatory diseases. By inhibiting IL-4 and IL-13, dupilumab decreases many of the mediators of type 2 inflammation (19). Dupilumab is used within multiple indications such as asthma, AD, PN and CRSwNP, and currently, dupilumab has been evaluated and recommended in Denmark by the Danish Medicines Council (DMC) in adults and adolescents with AD and children >6 years with AD. Dupilumab is the first and only targeted therapy indicated for infants 6 months to <6 years of age diagnosed with severe AD and provides a convenient dosing regimen as dupilumab is administered subcutaneously every 4 weeks with no loading dose. Dupilumab can be used with or without TCS. It should be used after optimal topical treatment but before systemic therapies such as methotrexate, azathioprine, cyclosporine and mycophenolate mofetil.

The efficacy and safety of dupilumab in infants 6 months to <6 years of age have been assessed in the LIBERTY AD PRESCHOOL trial that consists of two parts: part A and part B. Part A is an open-label, single-ascending-dose study staggered by age to evaluate the pharmacokinetics, efficacy and safety of dupilumab. Part B is a randomised, double-blind, parallel-group, placebo-controlled study comparing dupilumab in combination with low-potency TCS to placebo in combination with TCS for 16 weeks (20). The present application presents results from part B of the LIBERTY AD PRESCHOOL trial. In LIBERTY AD PRESCHOOL, [redacted] (≥75% improvement from baseline in the extent and severity of skin lesions) in the dupilumab + TCS group [redacted] vs the placebo + TCS group [redacted] at week 16. The least square (LS) mean difference in the percent change from baseline to week 16 in EASI score [redacted] In terms of SCORAD, the proportion of patients with SCORAD-50 (defined as ≥50% reduction in SCORAD from baseline at week 16) is presented in the current application. The proportion of patients with ≥50% reduction in SCORAD from baseline at week 16 [redacted] in the dupilumab + TCS group than in the placebo + TCS group, as [redacted] in the dupilumab + TCS group achieved SCORAD-50 compared to [redacted] The patient-oriented eczema measure (POEM) is also included in this application and the proportion of patients achieving an improvement of ≥3 points in POEM at week 16 was [redacted]. In terms of QoL, results from the children's dermatology life quality index (CDLQI) and the infants' dermatitis quality of life index (IDQOL) were presented [redacted] and the LS mean difference in change from baseline [redacted] The same was shown for IDQOL, [redacted]

[redacted]
[redacted]The LS mean difference in change from baseline was [redacted] The proportion of patients achieving a reduction of ≥3 points from baseline in the weekly average of daily worst scratch/itch NRS score at week 16 was also significantly improved in the dupilumab +TCS group with a risk ratio of [redacted]
[redacted]

Dupilumab was well tolerated in the LIBERTY AD PRESCHOOL trial, and [redacted]
[redacted] Most TEAEs were mild or moderate, resolved over time and were considered unrelated to study treatment. Only one patient in each group discontinued treatment due to an TEAE. Herpes infections were also assessed, [redacted]
[redacted] The number of patients with severe AD experiencing skin infections excluding herpes infections were [redacted] the placebo + TCS group. Eye-related disorders were also assessed, and the proportions of patients experiencing eye disorders [redacted] but the number of patients with both any treatment-emergent narrow-and broad-term conjunctivitis [redacted] in the placebo + TCS group. The risk of general disorders and administration site conditions during the 16-week treatment period [redacted]
[redacted]

The health economic analysis presented in this application is a cost analysis of treating children aged 6 months to <6 years of age with severe AD with dupilumab + TCS compared to placebo + TCS. This approach was preferential due to the inappropriateness of conducting a cost-utility analysis for this population. Measuring health-related quality of life (HRQoL) in children, especially children aged 6 months to <6 years has complexities and increases uncertainty in the estimates. No validated EQ-5D questionnaire exists for children <8 years of age (21), thus, no QoL measured with the EQ-5D questionnaire is available from the LIBERTY AD PRESCHOOL trial. Aside from the issues related to measuring QoL in children aged 6 months to <6 years, a cost analysis approach has been applied in all previous DMC evaluations of AD and the patient numbers within this age group are low as dupilumab has already been approved in children above the age of 6. The efficacy and safety of dupilumab in children aged 6 months to <6 years are similar to the efficacy and safety of dupilumab in the other indications where dupilumab has already been approved.

In the base case, the cost per patient for dupilumab was [redacted] for placebo. The incremental cost per patient was DKK 59,902 over a time horizon of 2 years. A budget impact analysis was also conducted to assess the budgetary impact of recommending dupilumab for children aged 6 months to <6 years with severe AD. Uncertainty in the input parameters in the cost model was explored through various sensitivity analyses and the parameters with the largest impact on the base case results were price of dupilumab, share of children achieving EASI50 at week 16 and time horizon. Changing the time horizon to 1 year resulted in the lowest incremental cost [redacted]

The aim of the budget impact analysis was to estimate the budgetary impact of recommending dupilumab as standard treatment for with severe AD (IGA = 4) in patients aged 6 months to <6 years. The budget impact was estimated per year in the first 5 years after the recommendation of dupilumab. The budget impact analysis compared the healthcare

expenditures in the two scenarios: the first where dupilumab is recommended as the standard treatment and the second where it is not. The total budget impact per year is the difference between the two scenarios. To determine the number of patients who could be candidates to dupilumab, a clinical expert with vast experience in treating children with AD was consulted. Based on the consultation, it was assumed there is currently 50 patients in Denmark that could be candidates. In addition, it was assumed that there will be 11 new candidates each year. It was further assumed that if dupilumab is recommended as standard treatment, 75% of the candidates will receive dupilumab, while 0% of patients will receive dupilumab if it is not recommended as standard of care. According to the analysis, the budget impact in year 1 and year 5 was estimated [redacted]., respectively.

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

5.1 The medical condition and patient population

5.1.1 Disease description

AD is a chronic type 2 immune-mediated inflammatory skin disease (2–5). The onset of AD typically begins in early infancy or childhood (around 60% of cases begin by 12 months of age) and can persist into adulthood in severe cases (4–8). AD is frequently the first step of the 'atopic march', where underlying type 2 inflammation leads to the development of further allergic disorders during infancy and childhood (3,5,9). AD is characterised by intense pruritus (itching), redness of skin, papules (pimples), excoriation (picking and scratching of the skin) and serous exudation (oozing) (3,22). Infants with AD experience a substantial symptom burden, with frequent comorbidities (23–32), and compared to adults, AD in infants tends to present at different sites, such as the face, extensor extremities and cheeks, and lesions are more often associated with oozing (3,33). AD also has a variable disease course with chronic relapses in some patients (4,5).

5.1.2 Pathophysiology of AD

The pathophysiology of AD is multifactorial, involving genetic factors (loss of skin barrier function), environmental triggers (allergens, chemicals, pollutants), microbial imbalance (Staphylococcus aureus colonisation) and immune dysregulation (type 2 inflammatory response) (2,34–38). The abnormal activation of the type 2 inflammatory pathway due to environmental triggers (presented in Figure 1) is a well-established pathophysiologic process underlying AD (19). Environmental triggers activate type 2 immune cells, which leads to overexpression of type 2 cytokines including IL-4, IL-5 and IL-13 and in turn the development of cutaneous inflammation and pruritis (35,36,38).

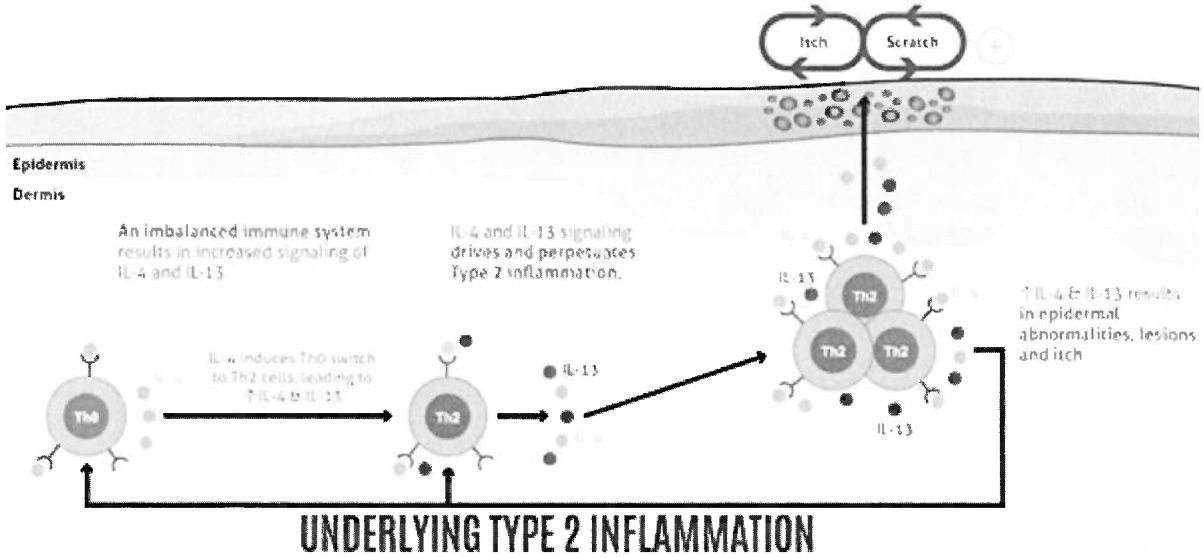


Figure 1: The type 2 inflammatory pathways underlying AD. Source: Biedermann et al. 2015 , Gandhi et al. 2016 ; Gittler et al. 2012 .

Figure note: AD = atopic dermatitis; IL = interleukin; Th0 = type 0 helper T cell; Th2 = type 2 helper T cell

5.1.3 Diagnosis and classification of AD

AD is diagnosed based on clinical, morphological and historical features (4). Various sets of criteria have been developed to aid the diagnosis of AD, but standardised diagnostic criteria are mostly used for research and clinical trial purposes, and the gold standard remains diagnosis by an experienced clinician (33). The UK Working Party has provided simple criteria which require itchy skin changes to be diagnosed within the previous 12 months, plus three of the following five criteria (41):

- onset of disease under the age of 2 years
- history of skin fold involvement
- generalised dry skin
- other atopic diseases
- visible flexural eczema

The severity of AD is commonly assessed with instruments such as the Eczema Area and Severity Index (EASI), Investigators Global Assessment (IGA) and the Scoring Atopic Dermatitis (SCORAD) index (4,42,43).

EASI is a highly validated instrument and stated as the preferred instrument for evaluating objective signs of AD by the expert group from Harmonising Outcome Measures for Eczema (HOME). The EASI score calculation is based on the physician's assessment of individual signs (erythema (E), induration/papulation (I), excoriation (X), and lichenification (L)), where each sign is scored as 0 = absent, 1 = mild, 2 = moderate, or 3 = severe, and also upon the 'area score' (the % body surface area (BSA) affected where 0 = 0% BSA, 1 = 1–9% BSA, 2 = 10–29% BSA, 3 = 30–49% BSA, 4 = 50–69% BSA, 5 = 70–89% BSA, 6 = 90–100% BSA. For each major section of the body (head, upper extremities, trunk and lower extremities), the EASI score is calculated as (E+I+X+L) x the area score. The total EASI score is the weighted total of the section using the weights as follows: the head and neck (H), upper extremities (U), trunk (T), and lower extremities (L) are assigned proportionate body surface areas of 20% (H), 20% (U), 30% (T), and 30% (L), roughly consistent with the 'rule of nines'. The minimum possible EASI score is 0, and the maximum possible EASI score is 72, with a higher score indicates increased extent and severity of AD. The EASI score of each sign (E, I, X and L) can be calculated in a similar way, for example, the EASI score of erythema = weighted sum of E x the area score at each section. The EASI scores are presented in Table 1.

Table 1: EASI scores for assessing AD disease severity. Source: Hanifin et al. 2022 (44).

Clear	Almost clear	Mild	Moderate	Severe	Very severe
0	0.1–1.0	1.1–7.0	7.1–21.0	21.1–50.0	50.1–72

The SCORAD is another validated tool used in clinical research and clinical practice that was developed to standardise the evaluation of the extent and severity of AD (42). There are three components to the assessment:

- A = extent of affected BSA, which is assessed as a percentage of each defined body area and reported as the sum of all areas, with a maximum score of 100%.
- B = severity of six specific symptoms of AD (redness, swelling, oozing/crusting, excoriation, skin thickening/lichenification, and dryness) is assessed using the following scale: none (0), mild (1), moderate (2), or severe (3), added up to a maximum of 18 total points.

- C = subjective symptoms of itching and sleeplessness are recorded for each symptom by the parent/caregiver or relative on a visual analog scale (VAS), where "0" is no itch (or sleeplessness) and "10" is the worst imaginable itch (or sleeplessness), with a maximum possible score of 20.

The subjective SCORAD is calculated as: A/5+7B/2+C, with a maximum possible score of 103. The objective SCORAD is calculated as A/5 + 7B/2 and the maximum objective SCORAD score is 83. Higher score indicates worse condition.

Table 2: SCORAD scores for assessing AD disease severity. Source: Faye et al. 2020 (45).

Mild	Moderate	Severe
>25	25–50	>50

The IGA assesses the overall severity of AD at a given time point and treatment success criterion is defined on a physician score of 0 or 1 on a 5-point scale (0 = clear: no inflammatory signs of AD. 1 = almost clear: barely perceptible erythema and/or minimal lesion elevation (papulation/infiltration). 2 = mild: visibly detectable, light pink erythema and very slight elevation (papulation/infiltration. 3 = moderate: dull red, clearly distinguishable erythema; clearly perceptible elevation (papulation/infiltration), but not extensive. 4 = severe: deep/dark red erythema; marked and extensive elevation (papulation/infiltration)) (46).
IGA is less frequently used in Denmark compared to EASI and SCORAD and is therefore considered less relevant in a Danish context; thus, IGA will not be described further.

5.1.4 Humanistic burden of AD

AD is associated with a substantial humanistic burden and has major implications on the QoL for both infants and children with AD and their caregivers and families. The intense pruritis leads to sleep disturbances and emotional stress, which impairs QoL substantially among infants with AD and their caregivers (3,10–16). Sleep disturbances among infants with AD are consistently reported in the published literature: In the UK Avon Longitudinal Study of Parents and Children (ALSPAC) with 13,988 participants, children with AD were more likely to experience worse sleep quality compared to children without AD at a range of time points between 2.5 years old and 10 years old (adjusted odds ratio: 1.48, 95% CI: 1.33, 1.66) (13). Overall, children with AD had an approximate 50% increased risk of sleep disturbances vs children without AD (adjusted odds ratio: 1.48, 95% CI: 1.33, 1.66). Increased disease severity and atopic comorbidities were significantly associated with poor sleep quality (13). In a US cross-sectional study, 76% of infants with severe AD and 34% of infants with moderate AD (aged 1 to 4 years, N=60) experienced sleep problems for five nights per week or more. Greater AD severity was associated with poorer sleep health (unstandardised regression coefficient [B] =1.22; p<0.01) and attention dysregulation (B=1.72; p<0.01). AD-related sleep disruptions led to significant impairments in playing and getting along with other children for children with moderate-to-severe AD vs mild AD (both p<0.01) (16). The burden of disease means that AD patients have lower chances of achieving various levels of educational attainment, from primary school to higher education (17).

As mentioned, AD does not just affect the children suffering from AD but also has a large impact on the children's caregivers and families. In the UK ALSPAC study of caregivers (N=11,649 mother-child pairs), mothers of infants with AD were significantly more likely to report difficulty falling asleep (adjusted odds ratio: 1.36, 95% CI: 1.01, 1.83), insufficient sleep (adjusted odds ratio: 1.43, 95% CI: 1.24, 1.66) and daytime exhaustion (adjusted odds ratio: 1.41, 95% CI: 1.12, 1.78) compared to mothers of children without AD. Mothers of infants with severe disease were more likely to report <6 hours sleep per night compared to mothers of infants with mild to moderate AD (adjusted odds ratio: 1.61, 95%: CI 1.05, 2.48) (12).

The association of AD with ADHD has been shown by a number of studies. A German study on children's mental health problems involving 2,916 infants found an association between AD and ADHD (18). The study found that infants with AD are at increased risk of mental health problems at age 10. Even if cleared afterward, eczema at age 1 to 2 years may cause persistent emotional and behavioural difficulties (18).

The prevalence of mental health disorders increases with increasing AD severity (47,48). A birth cohort study of 11,181 (49) participants that followed children from birth for a mean of 10 years found that the prevalence of symptoms of depression ranged from 6.0% to 21.6%. In addition, severe AD was associated with an approximately two-fold increase in risk of depression symptoms and internalising symptoms across childhood. As seen in Figure 2, the age-specific disability-adjusted life years (DALYs) and prevalence rates showed a right-skewed distribution, with a peak between 1 and 5 years of age. Females showed higher DALYs due to AD throughout all age groups. As the patients aged, AD DALYs decreased in both females and males. The prevalence rate of AD also initially decreased with age until the mid50s, in which it began increasing in both the sexes (50).

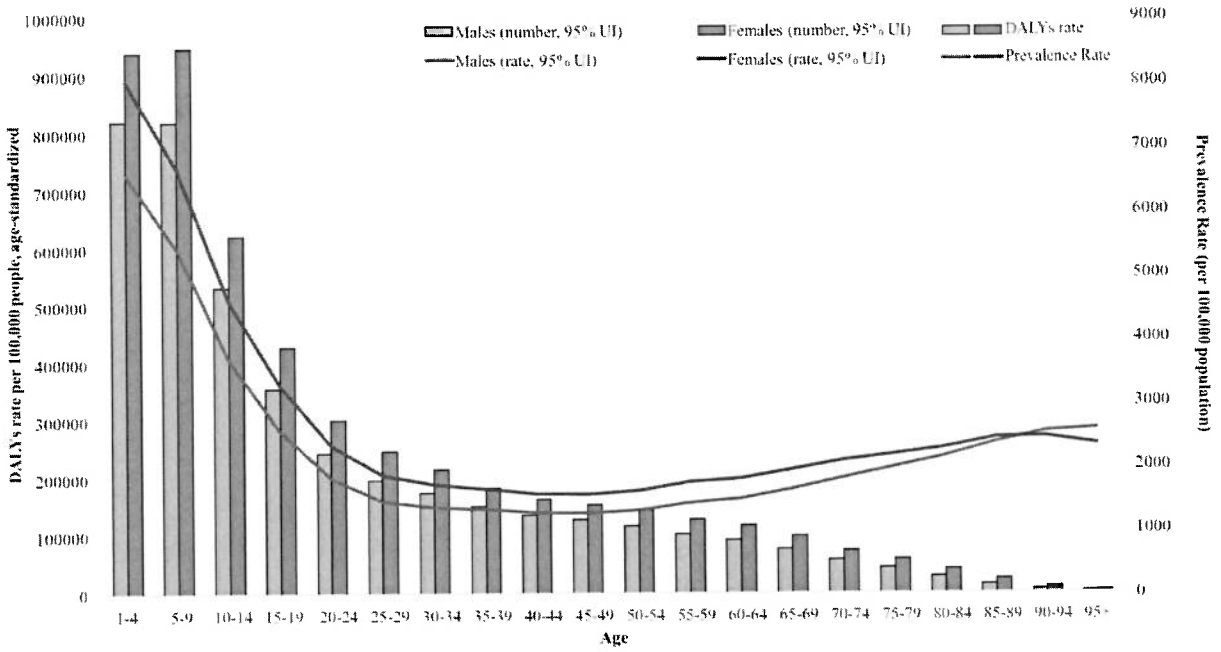


Figure 2: Global 2017 AD age-standardised DALYs per 100,000 people in males and females. The bars indicate DALYs rate, and the lines indicate prevalence rate. Source: Urban et al. 2021 (50).

Figure note: Abbreviations: DALY, Disability-adjusted life years: one measure of AD disease morbidity is through DALYs, measured as the years of life lost due to premature mortality plus the years lost due to disability or its consequences.

5.1.5 Prevalence and incidence of AD in children (6 months to <6 years)

The prevalence of AD generally ranges from 10% to 20% of the general infant population (6,51). In the EU, approximately 0.5% of infants (6 months to <6 years) have severe AD and are uncontrolled with topical therapy. AD is one of the most common chronic inflammatory dermatological conditions among the infant population, with an increasing proportion of patients suffering from moderate-to-severe AD as they age. The multinational cross-sectional Epidemiology of Children with Atopic Dermatitis Reporting on their Experience (EPI-CARE) study assessed the point

prevalence of AD in children aged 6 months to <6 years (51) and the study found the prevalence of infant AD to range from 7.1% in Germany to 18.7% in France.

Engebretsen et al. 2016 (52) assessed the onset of AD within the first 18 months of life in a large Danish birth cohort and found an overall prevalence of AD within the first 18 months of life to be 15% (7,942/52,950 children), with more cases among boys than girls (16.8% vs 13.1%, P<.0001). The prevalence of AD was higher in children born in urban municipalities (P<.0001) and by mothers with a high socio-occupational class (P< .0001) or a history of AD.
Eller et al. 2010 (53) assessed the relapsing pattern, sensitisation and prognosis of AD in the first 6 years in a population-based, prospective birth cohort from Denmark. The Danish Allergy Research Centre (DARC) cohort included 562 children with clinical examinations, specific-IgE and skin prick test at all follow-ups. The point-prevalence of AD peaked at 18 months of age (10%) and decreased at 36 and 72 months to slightly below 7%. The 6-year cumulative incidence was 22.8%.

Based on input from an advisory board, Sanofi expects the Danish prevalence of patients with severe AD who are 6 months to <6 years old to be around 50 to 80 patients, and the incidence is expected to be around 10 to 12 children each year. Currently, it is expected that 50 patients are candidates for dupilumab. A Danish clinical expert with vast experience in treating children with AD was consulted on the Danish prevalence and incidence of AD. The clinical expert found these estimates plausible in a Danish setting and informed that the development in the prevalence and incidence of AD in the patient population of interest has been constant over the last 5 years, and a stable prevalence and incidence are expected in the next 5 years. Please see the total number of new patients in the first 5 years in Table 3.

Table 3: Estimated number of new patients eligible for treatment

Year	1	2	3	4	5
Number of patients in Denmark who are expected to use dupilumab in the coming years	50	10-12	10-12	10-12	10-12

5.1.6 Patient populations relevant for this application

The indication from the European Medicines Agency (EMA) is treatment of children (6 months to <6 years) with severe AD who are candidates for systemic therapy. These children comprise the patient population relevant for this application.

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

According to the published literature, the main goals of AD management in infants are to control inflammation, improve symptoms such as pruritus and achieve long-term disease control; however, currently available treatments are symptom-relieving only (3). There are no published treatment guidelines specifically tailored to infants with AD aged 6 months to <6 years, and currently, no treatment options have been approved by the EMA for AD in infants. The European Task Force on Atopic Dermatitis (ETFAD) published recommendations in 2020 that include a stepwise approach to treatment of AD in paediatric patients (see Table 4) (33).

Table 4: EFTAD recommendations for the treatment of AD in children. Source: (33).

Severe: SCORAD >50 or persistent	Hospitalisation, systemic immunosuppression: cyclosporine A, methotrexate, azathioprine, mycophenolate mofetil (54,55). Systemic agents are recommended in patients with AD that is not adequately controlled by optimised topical regimens and phototherapy (56).
Moderate: SCORAD 25–50 or recurrent eczema	Proactive therapy with topical tacrolimus (5) or class II or class III topical glucocorticosteroids (55), wet wrap therapy, UV therapy although phototherapy is rarely used in prepubertal children, it is not contraindicated and its use depends rather on feasibility and equipment (5), psychosomatic counselling and climate therapy.
Mild: SCORAD <25 or transient eczema	Reactive therapy with topical glucocorticosteroids class II (5) or depending on local cofactors: topical calcineurin inhibitors (5), antiseptics including silver, silver-coated textiles. TCSs are important anti-inflammatory drugs to be used in AD, especially in the acute phase. TCIs are typically used as second-line therapy for the short-term, noncontinuous chronic treatment of moderate-to-severe AD in individuals who are non-immunocompromised and have failed to respond adequately to other topical prescription treatments for AD, or when those treatments are not advisable (4). TCIs are not indicated for use in children younger than 2 years.
Baseline: Basic therapy	Educational programmes, emollients, bath oils, avoidance of clinically relevant allergens (encasings, if diagnosed by allergy tests) (57–59).

The Danish Society of Dermatology (DDS) guidelines follow a four-step treatment guideline for children with AD (see Table 5). The nonpharmacological treatment of AD includes applying moisturising creams and baths. Bathing and use of anti-septic agents can reduce the amount of bacteria on the skin, while moisturising cream maintains hydration of the stratum corneum, which reduces dryness, micro fissures and prevents itch. Moisturising creams are recommended by the DDS as the only treatment for dry skin and mild eczema and as adjuvant treatment of moderate-to-severe AD. Used as adjuvant treatment, moisturising creams have shown to reduce the need for TCS and to increase the response to TCS treatment (60). TCS is the first choice of treatment for moderate-to-severe eczema, and most children are treated effectively with group I-II TCSs. Despite TCS being the mainstay of AD therapy, long-term use in infants is limited due to safety concerns, as TCS is associated with a range of local adverse events, particularly at higher doses (3,33). These adverse events include skin atrophy, acne, hypertrichosis (excessive hair growth) and exacerbations of skin infections (3). The risk of skin atrophy is a particular concern when treating thin-skin areas such as the face, neck, axillae, perineum, and intertriginous surfaces (where two skin areas may rub together). In rare cases, long-term TCS treatment can result in systemic adverse effects, such as hyperglycaemia, glaucoma, poor growth, hypertension, and adrenal insufficiency (3,61). Infants are at particular risk of systemic adverse effects compared with adults, due to their high body surface area-to-weight ratio (3,4).

The two TCIs tacrolimus and pimecrolimus are used in Denmark as a second choice of treatment and can be used on children above the age of two. The TCIs have anti-inflammatory effects as TCSs but do not induce skin atrophy and can be used long-term. However, TCIs are also associated with local adverse events, such as burning, stinging and pruritus. Additionally, concerns have been raised regarding their effects on the immune system and increased reports of malignancies, such as cutaneous lymphomas (3,55). Another treatment option is UV therapy, which should not be used as the only therapy but can be used as a supplement. UV therapy can be used for children with moderate-to-severe AD or when other treatments have not had the desired effect or when the quality of life is considerably reduced. UV therapy should not be used in the acute phases of AD but in the chronic phases. TCS and moisturising creams are recommended when the UV therapy is initiated to avoid exacerbations, but TCI should be avoided.

The only biologic treatment currently available for children with AD is dupilumab that is currently indicated for children (≥6 years) and adults with AD. Systemic therapies are available in Denmark but the systemic therapies such as cyclosporine A, methotrexate, azathioprine, mycophenolate mofetil are used off-label to treat AD and the use of these therapies is not appropriate for the treatment of infants and children due to toxicity. In addition, the evidence for the long-term efficacy of the systemic therapies is limited, and the systemic therapies are associated with safety concerns. The systemic therapies have been associated with serious adverse events such as infection, nephrotoxicity, pulmonary fibrosis, hepatic fibrosis and toxicity, bone marrow suppression, leucopenia, lymphoma and skin cancer (56,62–64). Children who receive treatment with off-label systemic therapies should be closely monitored by specialists with vast experience in systemic therapies. Systemic therapies should not be used alone but supplemented with TCS and/or TCI and moisturising creams. Cyclosporine A is the only systemic therapy beside dupilumab that is not used off-label for AD.

Table 5: DDS treatment recommendation for children with AD. Source: DDS (60).

Phase	Baseline: (Dry skin)	Mild to moderate: SCORAD <25	Moderate-to-severe: SCORAD 25-50	Severe refractory AD: SCORAD >50
Treatment recommendation	Basic skincare treatment, identification and management of unspecific and specific triggering factors	Low to moderate potency TCS and/or TCI	Moderate potency TCS and/or TCI. If remitting AD, proactive treatment is considered	Systemic treatment

Abbreviations: SCORAD: Scoring Atopic Dermatitis, TCI: Topical Calcineurin Inhibitors, TCS: topical corticosteroids.

5.2.2 Choice of comparator(s)

According to the DDS treatment guideline, TCSs are the first choice of treatment for moderate-to-severe AD where most children can be managed with low to moderate potency corticosteroids (I-II) (60). In addition, there are no published treatment guidelines specifically tailored to infants with AD aged 6 months to <6 years, and no treatment options have been approved by the EMA or the DMC for AD in infants, which means that all systemic treatments used in Denmark are used off-label for these patients. Therefore, the choice of comparator was based on the comparator arm in the LIBERTY AD PRESCHOOL trial, which was placebo in combination with TCS.

5.2.3 Description of the comparator

The comparator is placebo in combination with TCS as per the LIBERY AD PRESCHOOL, and no further information will be provided in this section.

5.3 The intervention

Dupilumab is the only fully human monoclonal antibody that inhibits both IL-4 and IL-13 signalling, which are the key central drivers of AD and other type 2 inflammatory diseases. By inhibiting IL-4 and IL-13, dupilumab decreases many of the mediators of type 2 inflammation (19). Currently, dupilumab has been evaluated and recommended in Denmark by the DMC in adults and for children and adolescents with AD >6 years.

Dupilumab is the first and only targeted therapy indicated for infants 6 months of age to <6 years diagnosed with severe AD and provides a convenient dosing regimen as dupilumab is administered subcutaneously every 4 weeks with no loading dose. Dupilumab can be used with or without TCS. Dupilumab should be used after optimal TCS but

dupilumab is expected to be positioned before the use of off-label systemic therapies such as methotrexate, azathioprine, cyclosporine and mycophenolate mofetil. For more information, see Table 6.

The present application addresses the use of dupilumab in infants at an early stage of the atopic march and a recent meta-analysis on allergic events across 12 dupilumab clinical trials indicates that early use of dupilumab can modify later in life outcomes, such as allergy, to a degree where the incidence of allergic events is lowered for subjects on dupilumab, and this reduction persists after subjects are off drug (65). Changing the course of developing other type 2 comorbidities would lower the needed healthcare utilisation for AD patients on dupilumab. In an editorial related to the above meta-analysis Dr. Bieber explains: "...At least in a subgroup of mainly adolescent patients with a particular clinical phenotype, a targeted therapy with a biologic directed against the T2 cytokines IL-4 and IL-13 has the potential to at least reduce the further development of atopic comorbidities during the observation time of these studies. This strongly suggests some plasticity of the T2 immune response in the atopic march until adolescence during which it seems still receptive for this kind of intervention. Assuming that the role of the T2 immune response may be even more dominant in younger patients, one may speculate that the attenuation effect reported in this study may be more significant when starting dupilumab in an earlier stage of the disease, i.e., in early childhood or even in infancy..."
"...The fact that patients who are receptive for attenuation of the atopic march in the present study are younger individuals with early onset and more severe forms of AD it would support the concept that severe skin inflammation is an important driving force in the mechanisms underlying the progress of the atopic march. Thus, efficiently reducing this inflammatory burden would be a crucial strategy to impact on the development of comorbidities. If this hypothesis is valid, further studies should confirm that attenuation of the atopic march in this subpopulation is associated with a long-term remission of AD after stopping the therapy. Another possible scenario would be a complete stop of the atopic march without significant long-term remission of AD..."

"...If further prospective studies, particularly in the pediatric population, confirm the impact of dupilumab on AD and the atopic march, it could become the first medicinal product to qualify as Disease Modifying Atopic Dermatitis Drug (DMADD) or a Disease Modifying Atopic March Drug (DMAMD)..." While not yet established, there are at least indications that use of dupilumab at an early stage of severe AD, will have benefits beyond that of just treating the AD in infancy/childhood.

Table 6: Description of dupilumab. Source: summary of product characteristics (SPC) on dupilumab (1).

Dosing	Dupilumab is dosed based on patients' weight: • ≥5 to <15 kg: 200 mg dupilumab subcutaneous every 4 weeks with no loading dose • ≥15 to <30 kg: 300 mg dupilumab subcutaneous every 4 weeks with no loading dose
Method of administration	Dupilumab is administered subcutaneously. The caregiver may administer dupilumab if the healthcare professional determines that this is appropriate. Proper training should be provided to caregivers on the preparation and administration of dupilumab prior to use. Dupilumab is administered 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
Treatment duration/criteria for treatment discontinuation	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 AD. Discontinuing treatment should be considered in patients who have shown no response after 16 weeks of treatment for AD

Should the pharmaceutical be administered with other medicines	No. However, dupilumab can be used with or without TCS. TCI may be used but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas (1)
Necessary monitoring, during administration, during the treatment period, and after the end of treatment	The need for continued therapy should be considered at least on an annual basis. The clinical expert was consulted regarding the need for blood tests during treatment with dupilumab. According to the clinical expert, it is not necessary to monitor patients with blood tests
Need for diagnostics or other tests (i.e., companion diagnostics)	None except the AD diagnosis

6. Literature search and identification of efficacy and safety studies

The efficacy and safety of dupilumab have been assessed in the LIBERTY AD PRESCHOOL (66). LIBERTY AD PRESCHOOL is a randomised, double-blind, placebo-controlled, parallel-group, phase 3 trial of dupilumab in combination with TCS compared to placebo in combination with TCS in patients aged 6 months to <6 years with moderate-to-severe AD. Since the LIBERTY AD PRESCHOOL trial is a head-to-head trial of dupilumab and placebo, no literature search was conducted in accordance with the DMC method guideline (67). Based on this, the headings in this section have been deleted.

7. Efficacy and safety

7.1 Efficacy and safety of dupilumab + TCS compared to placebo + TCS for children (6 months to <6 years) with severe AD

7.1.1 Relevant studies

The clinical study relevant for the assessment of dupilumab + TCS compared to placebo + TCS is the LIBERTY AD PRESCHOOL trial. A brief description of the LIBERTY AD PRESCHOOL trial will be provided in the following. Please see Appendix B for a detailed presentation of the main study characteristics and Appendix C for baseline characteristics of patients included in the study.

LIBERTY AD PRESCHOOL consists of two parts: part A and part B. Part A is an open-label, single-ascending-dose study staggered by age to evaluate the pharmacokinetics, efficacy and safety of dupilumab. Part B is a randomised, double-blind, parallel-group, placebo-controlled study comparing dupilumab in combination with low-potency TCS to placebo in combination with TCS for 16 weeks (20). The present application will present results from part B of the LIBERTY AD PRESCHOOL trial. Patients were eligible if aged 6 months to <6 years with moderate-to-severe AD diagnosed according to consensus criteria of the American Academy of Dermatology and had an inadequate response to TCS (66). Furthermore, the patient's baseline weekly average score for maximum scratch/itch intensity should have been ≥4, the IGA score at screening and baseline visits should have been ≥3, the EASI score at screening and baseline visits should have been ≥16, and the BSA involvement at screening and baseline visits should have been ≥10%. The trial consisted of the following 3 periods: a screening period of up to 56 days (including 2 weeks of TCS standardisation with low potency TCS), a treatment period of 16 weeks, and a follow-up period of 12 weeks (see [redacted] During the screening period, systemic treatments for AD were washed out, as applicable, according to the eligibility requirements.

[redacted]

Patients were randomly assigned (1:1) to subcutaneous placebo or dupilumab plus low-potency TCS (hydrocortisone acetate 1% cream) for 16 weeks. Randomisation was stratified by age, baseline bodyweight, and region. Patient allocation was done via a central interactive web response system, and treatment allocation was masked. Patients

received dupilumab based on bodyweight: ≥5 kg to <15 kg received 200 mg every 4 weeks, and ≥15 kg to <30 kg received 300 mg every 4 weeks. In the placebo group, patients were also dosed based on body weight: children ≥5 to <15 kg received 1.14 mL every 4 weeks, and children ≥15 to <30 kg received 2.0 mL every 4 weeks. Systemic immunomodulating treatments (e.g., ciclosporin, methotrexate, mycophenolate mofetil, and azathioprine), medium or higher potency TCS, crisaborole, and TCIs were prohibited but could be used as rescue for worsening disease at investigator's discretion after day 14. If rescue medication was topical, patients could continue their assigned study treatment, but if it was systemic, study treatment was permanently discontinued.

A total of 162 patients met eligibility criteria and were randomised to one of the two treatment groups: 79 to the placebo + TCS group and 83 to the dupilumab + TCS group (full analysis set, FAS). In total, 76 (96.2%) patients in the placebo + TCS group and 83 (100%) in the dupilumab + TCS group completed the week 16 visit (i.e., end of treatment visit). Three in the placebo + TCS group discontinued the study prior to week 16 (one patient each due to the patient being randomised in error, withdrawal of consent by the patient, and lost to follow-up). No patients in the dupilumab + TCS group discontinued the study. Overall, 19 (24.1%) in the placebo + TCS group and 19 (22.9%) in the dupilumab + TCS group entered the follow-up period (20). 62 patients in the placebo + TCS group and 63 patients in the dupilumab + TCS group had a baseline IGA = 4 defined as severe AD. Results from this subgroup of patients are presented in the following.

7.1.2 Efficacy – results from the LIBERTY AD PRESCHOOL trial

The LIBERTY AD PRESCHOOL trial is a head-to-head trial of dupilumab + TCS and placebo + TCS. Thus, direct comparative analyses are presented for all outcomes in this section. Results from the subgroup of severe AD patients (IGA = 4) are presented, as dupilumab is indicated for children (6 months to <6 years) with severe AD who are candidates for systemic therapy. Sanofi finds it relevant to present results on the following efficacy outcomes:

- Proportion of patients who achieve at least 75% eczema reduction on the EASI scale
- Mean reduction in EASI from baseline to week 16
- Proportion of patients who achieve at least a 50% eczema reduction on the SCORAD scale
- Proportion of patients who achieve an improvement of at least 3 points in POEM
- Mean change from baseline in CDLQI and IDQOL
- Proportion of patients who achieve a change of at least 3 points on the numerical rating scale

7.1.2.1 Results on 75% eczema reduction on the EASI scale

In part B of the LIBERTY AD PRESCHOOL trial, the proportion of patients achieving EASI-75 (defined as ≥75% improvement from baseline) at week 16 was a co-primary endpoint for the EU markets and EU reference markets. The EASI scoring system was described in section 5.1.3 and assessed at baseline and week 1, 2, 4, 8, 12 and 16. Values after first rescue treatment used were set to missing. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, adverse events (AEs) and lack of efficacy were considered non-responders. Patients with missing values of EASI score due to other reasons, including COVID-19, were imputed by multiple imputation (MI), and the response status was then derived. All non-missing data were used for MI. In MI, the seed numbers were 12345 and 54321 with imputation size 40.

The difference in proportions was calculated as dupilumab minus placebo and 95% confidence intervals (CI) were calculated using normal approximation. In the subgroup of patients with severe AD (IGA = 4), p-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by region (North America vs Europe) and baseline weight group [≥5–<15 kg vs ≥15–<30 kg).

[redacted] (≥75% improvement from baseline in the extent and severity of skin lesions) in the dupilumab + TCS group ([redacted] vs the placebo + TCS group [redacted] at week 16, with a treatment difference [redacted] which was sustained for the remainder of the treatment period, as seen in Figure 4. The relative difference was presented as a risk ratio (RR) of [redacted] Results are presented in Table 7 and Table 8.

Table 7: Proportion of patients with EASI-75 at week 16 (severe AD subgroup). Source: clinical study report (CSR) data on file (68).

	Dupilumab + TCS (N = 63)	Placebo + TCS (N = 62)
Proportion of patients with EASI-75, n (%, 95% CI)	[redacted]	[redacted]

Table 8: Absolute difference and relative difference in EASI-75 between dupilumab + TCS and placebo + TCS (FAS population, severe AD subgroup)

	Absolute difference in EASI-75	Relative difference in EASI-75
Dupilumab + TCS vs placebo + TCS (95% CI, p-value)	[redacted]	[redacted]

[redacted]

7.1.2.2 Mean reduction in EASI from baseline to week 16

The mean reduction in EASI from baseline to week 16 was a key secondary outcome in LIBERTY AD PRESCHOOL. Values after first rescue treatment used were set to missing. Patients with missing values at week 16 due to rescue

treatment, withdrawn consent, AEs and lack of efficacy were imputed by worst-observation-carried-forward (WOCF) or baseline value if there was no post-baseline value. Patients with missing values due to other reasons, including COVID-19, were imputed by MI. All non-missing data before imputation of WOCF were used for MI. In MI, the seed numbers were 12345 and 54321 with imputation size 40. The CI with p-value was based on treatment difference (dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomisation strata (region [North America vs Europe] and baseline weight group [≥5 to <15 kg vs ≥15–<30 kg]) as fixed factors.

The mean EASI score at baseline was similar across the two treatment groups. The LS mean percent change (reduction indicates improvement) from baseline to week 16 in EASI [redacted]. The LS mean difference in the percent change from baseline to week 16 in EASI score was [redacted] between the dupilumab + TCS group and the placebo + TCS group [redacted] Results are presented in Table 9.

Table 9: Percent change from baseline in EASI score at week 16 (severe AD subgroup). Source: CSR data on file (68).

	Dupilumab + TCS (N = 63)	Placebo + TCS (N = 62)
Observed/ Imputed subjects	[redacted]	[redacted]
Baseline mean (SD)	[redacted]	[redacted]
LS mean % change (SE)	[redacted]	[redacted]
95% CI of LS mean % change	[redacted]	[redacted]
Mean % change (SD)	[redacted]	[redacted]
LS mean difference (95% CI), p-value	[redacted]	

Table note: Abbreviations: CI=confidence interval; EASI=Eczema Area and Severity Index; FAS=full analysis set; LS=least squares; SE=standard error; SD=standard deviation; TCS=topical corticosteroids.

As shown in Figure 5, a treatment difference was observed as early as week 1 and was sustained for the remainder of the treatment period.

[redacted]

7.1.2.3 Proportion of patients who achieve at least a 50% eczema reduction on the SCORAD scale

The SCORAD is a validated tool in children and adults used in clinical research and clinical practice developed to standardise the evaluation of the extent and severity of AD (69). The SCORAD scoring system was described in section 5.1.3.

The proportion of patients with SCORAD-50 (defined as ≥50% reduction in SCORAD from baseline at week 16) was an exploratory efficacy outcome in LIBERTY AD PRESCHOOL and assessed at baseline and week 1, 2, 4, 8, 12 and 16. Values after first rescue treatment used were set to missing. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, AEs and lack of efficacy were considered non-responders. Patients with missing values of SCORAD score due to other reasons, including COVID-19, were imputed by MI, and the response status was then derived. All non-missing data were used for MI. In MI, the seed numbers were 12345 and 54321 with imputation size 40.

The difference in proportions was calculated as dupilumab + TCS minus placebo + TCS and 95% CI calculated using normal approximation. P-values were derived by CMH test stratified by region (North America vs Europe) and baseline weight group (5 to <15 kg vs ≥15–<30 kg).

The proportion of patients with ≥50% reduction in SCORAD from baseline at week 16 was higher in the dupilumab + TCS [redacted] Results are presented in Table 10 and Table 11.

Table 10: Proportion of patients with SCORAD-50 (≥50% reduction in SCORAD from baseline) at week 16 (severe AD subgroup). Source: CSR data on file (68).

	Dupilumab + TCS (N = 63)	Placebo + TCS (N = 62)
Proportion of patients with SCORAD-50, n (%, 95% CI)	[redacted]	[redacted]

Table 11: Absolute difference and relative difference in SCORAD-50 between dupilumab and placebo

	Absolute difference in SCORAD-50	Relative difference in SCORAD-50
Dupilumab + TCS vs placebo + TCS (95% CI, p-value)	[redacted]	[redacted]

7.1.2.4 Proportion of patients who achieve an improvement of at least 3 points in POEM

The POEM is recommended by HOME and is a 7-item, well-validated questionnaire used in clinical practice and clinical trials to assess disease symptoms in children and adults with atopic eczema (70). POEM consists of 7 items that evaluate the frequency of 7 symptoms (itch, sleep disturbance, dryness, flaking, weeping or oozing, bleeding and cracking) in the past 7 days, and the scores range from 0 to 28 (see Table 12) (71). For children, it is the caregiver's response to the 7 items that is assessed. All of the items carry equal weight and are scored from 0 to 4, i.e., a 5-point scale is used where 0 is no days, 1 is 1 to 2 days, 2 is 3 to 4 days, 3 is 5 to 6 days, and 4 is every day. A high score is indicative of a poor QoL.

Table 12: POEM scores (children). Source: Charman et al. 2004 (70).

0–2	3–7	8–16	17–24	25–28
Clear or almost clear	Mild eczema	Moderate eczema	Severe eczema	Very severe eczema

POEM was a secondary outcome in the LIBERTY AD PRESCHOOL trial assessed at week 2, 4, 8, 12 and 16 (66). Values after first rescue treatment used were set to missing. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, AEs and lack of efficacy were imputed by WOCF or baseline value if there was no post-baseline value. Patients with missing values due to other reasons, including COVID-19, were imputed by MI. All non-missing data before imputation of WOCF were used for MI. In MI, the seed numbers were 12345 and 54321 with imputation size 40. The CI was calculated using normal approximation, and the p-value was derived by CMH test stratified by region (North America vs Europe) and baseline weight group (5–<15 kg vs 15–30 kg).

The proportion of patients achieving an improvement of ≥3 points in POEM at week 16 [redacted] in the placebo + TCS group. The RR [redacted] Results are presented in Table 13 and Table 14.

Table 13: Proportion achieving an improvement of ≥3 points in POEM at week 16 (severe AD subgroup). Source: CSR data on file (68).

	Dupilumab + TCS (N = 63)	Placebo + TCS (N = 62)
Proportion achieving improvement ≥3 points in POEM total score, n (%, 95% CI)	[redacted]	[redacted]

Table 14: Absolute difference and relative difference in proportion achieving an improvement of ≥3 points in POEM at week 16 between dupilumab and placebo

	Absolute difference in POEM	Relative difference in POEM
Dupilumab + TCS vs placebo + TCS (95% CI, p-value)	[redacted]	[redacted]

7.1.2.5 Mean change from baseline in CDLQI and IDQOL

The CDLQI is a validated questionnaire designed to measure the impact of skin disease on the QoL in children ≥4 years of age (72). To complete the questionnaire, patients need to provide responses to 10 questions with focus on domains such as symptoms and feelings associated with disease (2 items); the impact of the disease on leisure (3 items); school and holidays (1 item); personal relationships (2 items); sleep (1 item); and the side effects of treatment for the skin disease (1 item). The instrument has a recall period of 7 days. The global score of the CDLQI for a patient is the sum of the score of each question with a maximum of 30 and a minimum of 0. The higher the score, the greater the impact is on the QoL.

The following CDLQI severity banding scores have been established for the effect of the disease on QoL (73):

- 0 to 1 = no effect on the child's life
- 2 to 6 = small effect
- 7 to 12 = moderate effect
- 13 to 18 = very large effect
- 19 to 30 = extremely large effect

The IDQOL is a validated questionnaire developed to measure the impact of skin disease on the QoL of infants and preschool children <4 years of age (74). The IDQOL is to be completed by the child's parent or caregiver. The questionnaire consists of 10 questions related to itching and scratching; mood of the child; how long it takes for the child to sleep; whether the eczema has interfered with the child's playing, swimming or participation in other family activities; problems during mealtimes; problems caused by treatment; level of comfort while dressing or undressing the child; and problems during bathing. Each question asks about the impact over the previous week. The IDQOL for a patient is the sum of the score of each question with a maximum of 30 and a minimum of 0. The higher the score, the greater the impact is on QoL.

For both CDLQI and IDQOL, values after first rescue treatment used were set to missing. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, AEs and lack of efficacy were imputed by WOCF or baseline value if there was no post-baseline value. Patients with missing values due to other reasons, including COVID-19, were imputed by MI. All non-missing data before imputation of WOCF were used for MI. In MI, the seed numbers were 12345 and 54321 with imputation size 40. The CI with p-value was based on treatment difference (dupilumab group vs placebo) of the LS mean change using ANCOVA model with baseline measurement as covariate and the treatment, randomisation strata (region [North America vs Europe] and baseline weight group) as fixed factors.

[redacted] The LS mean difference in change from baseline [redacted] in the dupilumab + TCS group compared to the placebo + TCS group [redacted] Results on CDLQI from the subgroup of patients with severe AD with patients aged ≥4 years old are presented Table 15.

Table 15: Change from baseline in CDLQI at week 16 (severe AD patients age ≥4 years old). Source: CSR data on file (68).

	Dupilumab + TCS (N = 37)	Placebo + TCS (N = 32)
Observed/ Imputed subjects	[redacted]	[redacted]
Baseline mean (SD)	[redacted]	[redacted]
LS mean change (SE)	[redacted]	[redacted]
95% CI of LS mean change	[redacted]	[redacted]
LS mean difference (95% CI), p-value	[redacted]	

Abbreviations: CDLQI=Children's Dermatology Life Quality Index; CI=confidence interval; FAS=full analysis set; LS=least squares; SE=standard error; TCS=topical corticosteroids.

In IDQOL, [redacted] The LS mean difference in change from baseline [redacted] in the dupilumab + TCS group compared to the placebo + TCS group [redacted] Results on IDQOL from the subgroup of patients with severe AD with patients aged <4 years old are presented Table 16.

Table 16: Change from baseline in IDQOL at week 16 (severe AD patients age <4 years old). Source: CSR data on file (68).

	Dupilumab + TCS (N = 26)	Placebo + TCS (N = 30)
Observed/ Imputed subjects	[redacted]	[redacted]
Baseline mean (SD)	[redacted]	[redacted]
LS mean change (SE)	[redacted]	[redacted]
95% CI of LS mean change	[redacted]	[redacted]
LS mean difference (95% CI), p-value	[redacted]	

Abbreviations: CI=confidence interval; FAS=full analysis set; IDQOL= Infants' Dermatology Quality of Life Index; LS=least squares; SE=standard error; TCS=topical corticosteroids.

7.1.2.6 Proportion of patients who achieve a change of at least three points on the numerical rating scale

The numerical rating scale (NRS) measures itch using a worst scratch/itch NRS that was developed and tested for the study-relevant age group. This is an 11-point scale (0 to 10) in which 0 indicates no scratching/itching, while 10 indicates worst scratching/itching possible. Patients are asked to rate the intensity of their itch in the last 24 hours using this scale. The NRS can be interpreted as follows:

- NRS = 0 – no pruritus
- NRS <3 – mild pruritus

- NRS >3 to < 7 – moderate pruritus
- NRS >7 to <9 – severe pruritus
- NRS >9 – very severe pruritus

Parents/caregivers are instructed in using the scale to record their child's pruritus score at the screening visit. Using the e-diary, parents/caregivers complete the rating scale daily throughout the entire study (screening, treatment and follow-up periods). The baseline worst scratch/itch scale score is defined as the prorated average of the worst scratch/itch scale scores reported continuously for 7 days right before the baseline visit (i.e., study day -7 to day -1). For post-baseline worst itch scale score, the weekly mean of daily worst scratch/itch score is calculated as the average of the available reported daily worst scratch/itch score within the week.

The proportion of patients achieving a reduction of ≥3 points from baseline in the weekly average of daily worst scratch/itch NRS score at week 16 was a key secondary outcome in the LIBERTY AD PRESCHOOL trial. In the subgroup of patients with severe AD, the proportion of patients with improvement (reduction) worst scratch/itch NRS ≥3 from baseline at week 16 was [redacted] in the placebo + TCS group. The relative difference expressed as a RR [redacted] in favour of dupilumab. Results are presented in Table 17 and Table 18.

Table 17: Proportion of patients with reduction of worst scratch/itch NRS ≥3 from baseline at week 16 (severe AD subgroup). Source: CSR data on file (68).

	Dupilumab + TCS (N = 63)	Placebo + TCS (N = 62)
Proportion of patients with improvement (reduction) worst scratch/itch NRS ≥3, n (%)	[redacted]	[redacted]

Table 18: Absolute difference and relative difference in improvement (reduction) of worst scratch/itch NRS ≥3 from baseline at week 16

	Absolute difference	Relative difference
Dupilumab + TCS vs placebo + TCS (95% CI)	[redacted]	[redacted]

7.1.3 Safety – results per study

Sanofi finds it relevant to present results on the following safety outcomes:

- Proportion of patients who experience at least one AE and at least one SAE;
- Proportion of patients who experience a herpes infection;
- Proportion of patients who discontinue treatment due to AEs;
- Proportion of patients experiencing skin infections (excluding herpes infections);
- Proportion of patients with at least one eye related event; and
- Proportion of patients with general disorders and administration site conditions.

In the following, results from the subgroup of patients in the safety analysis set (SAF) with baseline IGA = 4 are presented. The SAF comprised 78 patients in the placebo + TCS arm and 83 patients in the dupilumab + TCS arm. 78.2% (61 patients) and 75.9% (63 patients) had a baseline IGA = 4 in the placebo + TCS arm and dupilumab + TCS arm, respectively.

7.1.3.1 Proportion of patients with at least one adverse event and one serious adverse event

AEs and serious adverse events (SAEs) were collected starting from the time of informed consent signature and at each visit until the end of the study. All AEs are to be coded to a "Preferred Term (PT)", "High Level Term (HLT)" and associated primary "System Organ Class (SOC)" according to the Medical Dictionary for Regulatory Activities (MedDRA).

Overall, dupilumab was well tolerated in the LIBERTY AD PRESCHOOL trial, [redacted] Most TEAEs were mild or moderate, resolved over time and were considered unrelated to study treatment. Results are summarised in Table 19, and the absolute and relative differences are presented in Table 20.

Table 19: Proportion with at least one TEAE and one SAE (severe AD subgroup). Source: CSR data on file (68).

	Dupilumab + TCS (N = 63)	Placebo + TCS (N = 61)
Proportion of patients with at least one TEAE	[redacted]	[redacted]
Proportion of patients with at least one SAE	[redacted]	[redacted]

*The 95% CI were calculated with Clopper-Pearson's exact method.

Table 20: Absolute and relative differences in safety outcomes between dupilumab and placebo

	Absolute differences	Relative differences
Proportion of patients with at least one TEAE	[redacted]	[redacted]
Proportion of patients with at least one SAE	[redacted]	[redacted]

*0.5 was added to the proportion of patients with at least one SAE in the dupilumab group to calculate the relative risk, as 0 events were observed for dupilumab.

7.1.3.2 Proportion of patients who discontinue treatment due to AEs

During the 16-week treatment period, [redacted] Results are presented in Table 21 and Table 22.

Table 21: Proportion of patients who discontinue in LIBERTY AD PRESCHOOL (severe AD subgroup). Source: CSR data on file (68).

	Dupilumab (N = 63)	Placebo (N = 61)
Any TEAE leading to permanent discontinuation of study drug	[redacted]	[redacted]

*The 95% CI were calculated with Clopper-Pearson's exact method.

Table 22: Absolute and relative differences in discontinuation between dupilumab and placebo

	Absolute differences	Relative differences
Any TEAE leading to discontinuation of study drug permanently	[redacted]	[redacted]

7.1.3.3 Proportion of patients who experience a herpes infection

In the severe AD subgroup, very few herpes infections were observed [redacted] The RR for a herpes virus infection was [redacted] between dupilumab and placebo. The RR for herpes simplex and oral herpes was [redacted] respectively. Results are presented in Table 23, and the absolute and relative differences are presented in Table 24.

Table 23: Proportion of patients with a herpes infection (severe AD subgroup). Source: CSR data on file (68).

	Dupilumab (N = 63)	Placebo (N = 61)
Proportion of patients with a herpes virus infection	[redacted]	[redacted]
Proportion of patients with herpes simplex	[redacted]	[redacted]
Proportion with oral herpes	[redacted]	[redacted]

*The 95% CI were calculated with Clopper-Pearson's exact method.

Table 24: Absolute and relative differences in herpes infections between dupilumab and placebo

	Absolute differences	Relative differences
Proportion of patients with a herpes virus infection	[redacted]	[redacted]
Proportion of patients with herpes simplex	[redacted]	[redacted]
Proportion with oral herpes	[redacted]	[redacted]

*[redacted]

7.1.3.4 Proportion of patients experiencing skin infections (excluding herpes infections)

The number of patients with severe AD experiencing skin infections excluding herpes infections was [redacted] the placebo + TCS group. The skin infections were as follows [redacted] demonstrating that dupilumab reduces the risk of skin infections compared to placebo. Results are presented in Table 25 and Table 26.

Table 25: Proportion of patients with skin infections excluding herpes infections in LIBERTY AD PRESCHOOL (severe AD subgroup). Source: CSR data on file (68).

	Dupilumab + TCS (N = 63)	Placebo + TCS (N = 61)
Proportion with skin infections (adjudicated) excluding herpes infections during the 16-week treatment period	[redacted]	[redacted]

Table 26: Absolute and relative differences in skin infections excluding herpes infections between dupilumab and placebo

	Absolute differences	Relative differences
Skin infections excluding herpes infections	[redacted]	[redacted]

7.1.3.5 Proportion of patients with at least one eye-related event

The number of patients with at least on eye-related event during the 16-week treatment period in patients with severe AD [redacted] in the placebo + TCS group. In the dupilumab + TCS group, [redacted] Results are presented in Table 27 and Table 28.

Table 27: Proportion of patients with eye disorders in LIBERTY AD PRESCHOOL (severe AD subgroup). Source: CSR data on file (68).

	Dupilumab + TCS (N = 63)	Placebo + TCS (N = 61)
Proportion experiencing eye disorders	[redacted]	[redacted]

*The 95% CI were calculated with Clopper-Pearson's exact method.

Table 28: Absolute and relative differences in proportion with eye disorders between dupilumab and placebo

	Absolute differences	Relative differences
Differences in eye disorders	[redacted]	[redacted]

AEs of conjunctivitis were assessed using both a broad customised MedDRA query (CMQ) containing 16 terms and a narrow standardised MedDRA query (SMQ) containing 5 terms that included "Conjunctivitis" that were used to analyse events of conjunctivitis. Broad conjunctivitis comprised: conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, atopic keratoconjunctivitis, blepharitis, dry eye, eye irritation, eye pruritus, lacrimation increased, eye discharge, foreign body sensation in eyes, photophobia, xerophthalmia, ocular hyperaemia and conjunctival hyperaemia. Narrow conjunctivitis comprised: conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral and atopic keratoconjunctivitis. In patients with severe AD, the number of patients with both any treatment-emergent narrow and broad conjunctivitis [redacted]) in the placebo + TCS group. Results are presented in Table 29 and Table 30.

Table 29: Proportion of patients with AE of conjunctivitis (both narrow and broad term) in LIBERTY AD PRESCHOOL (severe AD subgroup). Source: CSR data on file (68).

	Dupilumab + TCS (N = 63)	Placebo + TCS (N = 61)
AE of conjunctivitis (both narrow and broad term)	[redacted]	[redacted]

*The 95% CI were calculated with Clopper-Pearson's exact method.

Table 30: Absolute and relative differences in AE of conjunctivitis (both narrow and broad term) between dupilumab and placebo

	Absolute differences	Relative differences
AE of conjunctivitis (both narrow and broad term)	[redacted]	[redacted]

*0.5 was added to the placebo group to calculate the relative risk, as 0 events were observed for placebo.

7.1.3.6 Proportion of patients with general disorders and administration site conditions

The number of patients with general disorders and administration site conditions during the 16-week treatment period in patients with severe AD was [redacted] in the placebo + TCS group. In the dupilumab + TCS group, the 3 [redacted] with dupilumab compared to placebo. Results are presented in Table 31 and Table 32.

Table 31: Proportion of patients with general disorders and administration site conditions in LIBERTY AD PRESCHOOL (severe AD subgroup). Source: CSR data on file (68).

	Dupilumab + TCS (N = 63)	Placebo + TCS (N = 61)
Proportion experiencing general disorders and administration site conditions	[redacted]	[redacted]

*The 95% CI were calculated with Clopper-Pearson's exact method.

Table 32: Absolute and relative differences in general disorders and administration site conditions between dupilumab and placebo

	Absolute differences	Relative differences
General disorders and administration site conditions	[redacted]	[redacted]

7.1.3.7 Summary of TEAEs in the severe AD population from LIBERTY AD PRESCHOOL

A summary of the TEAEs from the LIBERTY AD PRESCHOOL trial in the severe AD population is presented in **Error! Reference source not found.**. Common TEAEs that occurred with a higher frequency in the placebo + TCS group than in the dupilumab + TCS group were [redacted].

Table 33: Summary of TEAEs in patients with severe AD (IGA = 4) during the 16-week treatment period categorised as mild, moderate or severe intensity (severe AD subgroup). Source: CSR data on file.

Safety Analysis Set - Patients with baseline IGA = 4	Placebo + TCS (N = 61)	Dupilumab + TCS (N = 63)
Number of patients with any TEAE, n (%)	[redacted]	[redacted]
Patients with TEAE leading to treatment discontinuation	[redacted]	[redacted]
MILD, n (%)	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Molluscum contagiosum	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Conjunctivitis	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Gastroenteritis viral	[redacted]	[redacted]

Safety Analysis Set - Patients with baseline IGA = 4	Placebo + TCS (N = 61)	Dupilumab + TCS (N = 63)
Bronchitis	[redacted]	[redacted]
Croup infectious	[redacted]	[redacted]
Dermatitis infected	[redacted]	[redacted]
Impetigo	[redacted]	[redacted]
Keratitis viral	[redacted]	[redacted]
Pustule	[redacted]	[redacted]
Skin infection	[redacted]	[redacted]
Varicella	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Ear infection	[redacted]	[redacted]
Eczema herpeticum	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]
Herpes simplex	[redacted]	[redacted]
Oral herpes	[redacted]	[redacted]
Otitis media acute	[redacted]	[redacted]
Paronychia	[redacted]	[redacted]
Pharyngitis	[redacted]	[redacted]
Respiratory tract infection viral	[redacted]	[redacted]
Skin bacterial infection	[redacted]	[redacted]
Staphylococcal infection	[redacted]	[redacted]
Staphylococcal skin infection	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Dermatitis atopic	[redacted]	[redacted]
Angioedema	[redacted]	[redacted]
Erythema	[redacted]	[redacted]

Safety Analysis Set - Patients with baseline IGA = 4	Placebo + TCS (N = 61)	Dupilumab + TCS (N = 63)
Hair growth abnormal	[redacted]	[redacted]
Madarosis	[redacted]	[redacted]
Nail dystrophy	[redacted]	[redacted]
Perioral dermatitis	[redacted]	[redacted]
Skin burning sensation	[redacted]	[redacted]
Urticaria	[redacted]	[redacted]
Blister	[redacted]	[redacted]
Cold urticaria	[redacted]	[redacted]
Dermatitis contact	[redacted]	[redacted]
Idiopathic urticaria	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Dental caries	[redacted]	[redacted]
Abdominal discomfort	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Lip swelling	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Asthma	[redacted]	[redacted]
Rhinorrhoea	[redacted]	[redacted]
Epistaxis	[redacted]	[redacted]
Adenoidal hypertrophy	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Dysphonia	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]
Rhinitis allergic	[redacted]	[redacted]

Safety Analysis Set - Patients with baseline IGA = 4	Placebo + TCS (N = 61)	Dupilumab + TCS (N = 63)
Tonsillar hypertrophy	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Lymphadenopathy	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Dermatopathic lymphadenopathy	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Injection site erythema	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Injection site oedema	[redacted]	[redacted]
Injection site urticaria	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Foot deformity	[redacted]	[redacted]
Growing pains	[redacted]	[redacted]
Knee deformity	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]
Blepharitis	[redacted]	[redacted]
Conjunctivitis allergic	[redacted]	[redacted]
Eye irritation	[redacted]	[redacted]
Eye swelling	[redacted]	[redacted]
Eyelid oedema	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Skin laceration	[redacted]	[redacted]
Contusion	[redacted]	[redacted]
Investigations	[redacted]	[redacted]

Safety Analysis Set - Patients with baseline IGA = 4	Placebo + TCS (N = 61)	Dupilumab + TCS (N = 63)
SARS-CoV-2 test positive	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	[redacted]	[redacted]
Skin papilloma	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Nightmare	[redacted]	[redacted]
Irritability	[redacted]	[redacted]
Congenital, familial and genetic disorders	[redacted]	[redacted]
Cryptorchism	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]
Cerumen impaction	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Headache	[redacted]	[redacted]
MODERATE, n (%)	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]
Coronavirus infection	[redacted]	[redacted]
Gastroenteritis viral	[redacted]	[redacted]
Herpes virus infection	[redacted]	[redacted]
Impetigo	[redacted]	[redacted]
Otitis media	[redacted]	[redacted]

Safety Analysis Set - Patients with baseline IGA = 4	Placebo + TCS (N = 61)	Dupilumab + TCS (N = 63)
Paronychia	[redacted]	[redacted]
Varicella	[redacted]	[redacted]
Abscess limb	[redacted]	[redacted]
Ear infection	[redacted]	[redacted]
Genital candidiasis	[redacted]	[redacted]
Herpes simplex	[redacted]	[redacted]
Otitis media acute	[redacted]	[redacted]
Respiratory syncytial virus infection	[redacted]	[redacted]
Skin infection	[redacted]	[redacted]
Staphylococcal abscess	[redacted]	[redacted]
Staphylococcal skin infection	[redacted]	[redacted]
Viral upper respiratory tract infection	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Dermatitis atopic	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]
Dermatitis	[redacted]	[redacted]
Erythema	[redacted]	[redacted]
Onycholysis	[redacted]	[redacted]
Urticaria	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Dental caries	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]
Food allergy	[redacted]	[redacted]

Safety Analysis Set - Patients with baseline IGA = 4	Placebo + TCS (N = 61)	Dupilumab + TCS (N = 63)
Milk allergy	[redacted]	[redacted]
Hypersensitivity	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Eosinophilia	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Lip injury	[redacted]	[redacted]
Joint dislocation	[redacted]	[redacted]
Skin laceration	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
White blood cell count increased	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Asthma	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Wheezing	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
SEVERE, n (%)	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Eosinophilia	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]

Safety Analysis Set - Patients with baseline IGA = 4	Placebo + TCS (N = 61)	Dupilumab + TCS (N = 63)
Blepharitis	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Cellulitis staphylococcal	[redacted]	[redacted]
Dermatitis infected	[redacted]	[redacted]
Staphylococcal bacteraemia	[redacted]	[redacted]
Staphylococcal skin infection	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Head injury	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Dermatitis atopic	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]

7.1.4 Comparative analyses of efficacy and safety

The LIBERTY AD PRESCHOOL trial is a head-to-head trial of dupilumab + TCS and placebo + TCS with data on all relevant outcomes. No comparative analyses are presented in this section in accordance with the DMC method guideline (67). Please see comparative results in section 7.1.2 and 7.1.3.

8. Health economic analysis

The health economic analysis was a cost analysis of treating children aged 6 months to <6 years with severe AD with dupilumab + TCS compared to placebo + TCS. This approach was preferential due to the inappropriateness of conducting a cost-utility analysis for this population. Measuring health-related quality of life (HRQoL) in children, especially children aged 6 months to <6 years has complexities and increases uncertainty in the estimates. No validated EQ-5D questionnaire exists for children <8 years of age (21), thus, no QoL measured with the EQ-5D questionnaire is available from the LIBERTY AD PRESCHOOL trial. Aside from the issues related to measuring QoL in children aged 6 months to <6 years, a cost analysis approach has been applied in all previous DMC evaluations of AD and the patient numbers within this age group are low as dupilumab has already been approved in children above the age of 6. The efficacy and safety of dupilumab in children aged 6 months to <6 years are similar to the efficacy and safety of dupilumab in the other indications where dupilumab has already been approved. Uncertainty in the cost parameters included in the analysis was assessed with deterministic one-way sensitivity analyses (DSA) and scenario analyses. A budget impact analysis was also conducted to assess the budgetary impact of recommending dupilumab for children aged 6 months to <6 years with severe AD.

8.1 Model

The applied model was a cost model developed in Excel. In the model, the cost per patient of treating children with severe AD with dupilumab + TCS and placebo + TCS was estimated. The cost model applied a limited societal perspective in accordance with DMC guidelines and costs incurred after the first year were discounted by 3.5% per year (75). All relevant costs associated with treating children with severe AD in a Danish clinical setting were included (see section 8.5). Information on the Danish clinical practice for treating these patients primarily came from consultation of a clinical expert (see section 11). Half-cycle correction was not implemented in the model due to the short cycle length (weekly cycles).

The time horizon of the model was 2 years in the base case. The rationale for the time horizon is that the clinical expert expects that patients aged 6 months to <6 years will be treated for approximately 2 years with a biologic agent before treatment is discontinued. Furthermore, the median age in the LIBERTY AD PRESCHOOL trial is 4 years. It is expected that once patients turn 6, they are included in the dupilumab indication for patients ≥6 to 11 years of age. As treatment regimens for children aged >6 years are not included in the model, the model should not be used to estimate the costs for patients above 6 years of age (e.g., if the median age of the children in the target population is 4 years, the costs should only be estimated for maximum 2 years).

In the model, patients can only discontinue dupilumab treatment if they do not achieve EASI50 (partial response) after 16 weeks of treatment. In a Danish clinical setting, the definition of partial response might differ slightly from the definition in the model. The clinical expert expects that partial response will most likely be defined as achieving EASI50 combined with a reduction of 4 points in the dermatology life quality index (DLQI) in a Danish clinical setting, i.e., the same definition as for patients age 12 years or above according to DDS guideline (60). However, it was assumed that defining partial response as EASI50 was still relevant in a Danish setting.

Patients discontinuing from dupilumab continue to receive TCS. It is not possible to discontinue placebo treatment in the model.

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

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

Since the model was a cost model, no efficacy outcomes or health state utilities have been included. However, some inputs were used in the model, and these are presented in Table 34.

Table 34: Input data used in the model

Name of estimates	The LIBERTY AD PRESCHOOL trial	Input value used in the model	How is the input value obtained/estimated?
Share of patients below 15 kg	[redacted]	[redacted]	Obtained from CSR for the LIBERTY AD PRESCHOOL trial
Drop-out rate (EASI50 at week 16)	[redacted]	[redacted]	Obtained from CSR for the LIBERTY AD PRESCHOOL trial. It was assumed based on consultation of the clinical expert that patients who are not partial responders (defined as EASI50) at week 16 discontinue treatment
Share of patients who can self-administer dupilumab	Not applicable	95%	The clinical expert expects that in clinical practice, 95% of patients can self-administer dupilumab at home after the first 2 doses, while <5% of patients will be administered at the hospital
Rate of flares	Flares were not assessed in the LIBERTY AD PRESCHOOL trial	[redacted]	The flare rates used in the model were informed by the clinical expert (see how the estimates were calculated in section 8.5.2)
Blood tests	Patients in the LIBERTY AD PRESCHOOL trial had blood tests performed continuously throughout the study period	0 blood tests	According to the clinical expert, no blood tests are performed in the clinical setting

Name of estimates	The LIBERTY AD PRESCHOOL trial	Input value used in the model	How is the input value obtained/estimated?
Share of patients experiencing conjunctivitis	[redacted]	[redacted]	AEs in the first 16 weeks were from the LIBERTY AD PRESCHOOL trial, and the rates for the first year and the following years were calculated based on the rate for the first 16 weeks, as it was assumed that the risks were continued during all treatment years
Share of patients experiencing molluscum contagiosum	[redacted]	[redacted]	AEs in the first 16 weeks were from LIBERTY AD PRESCHOOL, and the rates for the first year and the following years were calculated based on the rate for the first 16 weeks, as it was assumed that the risks were continued during all treatment years
Share of patients experiencing impetigo	[redacted]	[redacted]	AEs in the first 16 weeks were from the LIBERTY AD PRESCHOOL trial, and the rates for the first year and the following years were calculated based on the rate for the first 16 weeks, as it was assumed that the risks were continued during all treatment years

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

8.2.2.1 Patient population

The Danish patient population

The characteristics of the Danish patients aged 6 months to <6 years with severe AD were discussed with the clinical expert who found the patient population with severe AD (IGA = 4) from the LIBERTY AD PRESCHOOL trial to be comparable to the Danish patient population.

Patient population in the clinical documentation submitted

The baseline characteristics of the patient population in LIBERTY AD PRESCHOOL with severe AD (IGA = 4) are presented in Table 55. [redacted]

Patient population in the health economic analysis submitted

The patient population included in the cost model was based on the patient population in the LIBERTY AD PRESCHOOL trial with severe AD (baseline IGA = 4).

Table 35: Patient population

Patient population Important baseline characteristics	Clinical documentation	Used in the model (number/value including source)	Danish clinical practice (including source)
Age (years)			
Mean (SD)	[redacted]	[redacted]	Similar to the population from LIBERTY AD PRESCHOOL
Median	[redacted]	[redacted]	Similar to the population from LIBERTY AD PRESCHOOL
Sex, n (%)			
Male	[redacted]	[redacted]	Similar to the population from LIBERTY AD PRESCHOOL
Female	[redacted]	[redacted]	Similar to the population from LIBERTY AD PRESCHOOL
Race, n (%)			
White	[redacted]	[redacted]	Similar to the population from LIBERTY AD PRESCHOOL
Black or African American	[redacted]	[redacted]	Similar to the population from LIBERTY AD PRESCHOOL
Other	[redacted]	[redacted]	Similar to the population from LIBERTY AD PRESCHOOL
Weight (kg)			
Mean (SD)	[redacted]	[redacted]	Similar to the population from LIBERTY AD PRESCHOOL

Patient population Important baseline characteristics	Clinical documentation	Used in the model (number/value including source)	Danish clinical practice (including source)
Median	[redacted]	[redacted]	Similar to the population from LIBERTY AD PRESCHOOL
Baseline weight group, n (%)			
≥5 to <15 kg	[redacted]	[redacted]	Similar to the population from LIBERTY AD PRESCHOOL
≥15 to <30 kg	[redacted]	[redacted]	Similar to the population from LIBERTY AD PRESCHOOL

8.2.2.2 Intervention: dupilumab

Dupilumab as expected in Danish clinical practice

Dupilumab is expected to be indicated for children aged 6 months to <6 years with severe AD who are candidates to systemic therapy after optimal topical treatment. Dupilumab is expected to be positioned before the off-label systemic treatments currently used for AD such as cyclosporine, methotrexate, azathioprine and mycophenolate mofetil. Dupilumab should be dosed the same way as in the LIBERTY AD PRESCHOOL trial, i.e., based on patients' weight: ≥5 to <15 kg received 200 mg every 4 weeks with no loading dose, and patients ≥15 to <30 kg received 300 mg every 4 weeks with no loading dose.

Dupilumab in the clinical documentation submitted

In LIBERTY AD PRESCHOOL, dupilumab was administered subcutaneously, and the dose was based on patients' weight: ≥5 to <15 kg received 200 mg every 4 weeks with no loading dose, and patients ≥15 to <30 kg received 300 mg every 4 weeks with no loading dose. The subcutaneous injections alternate between the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms so that the same site is not injected for 2 consecutive administrations. The mean (SD) duration of exposure was 112.1 days (7.84) in the dupilumab + TCS group in the SAF population (not limited to severe AD). The mean injection compliance with dupilumab was approximately 99%.

Dupilumab as in the health economic analysis submitted

Dupilumab was administered subcutaneously in the model, and the dose was based on patients' weight: ≥5 to <15 kg received 200 mg dupilumab every 4 weeks with no loading dose, and patients ≥15 to <30 kg received 300 mg dupilumab every 4 weeks with no loading dose. The clinical expert expects patients within the current indication to be treated for 2 years, and then dupilumab will be discontinued. In the model, patients would only discontinue dupilumab if they did not achieve EASI50 after 16 weeks of treatment. It was assumed that patients discontinuing on dupilumab would continue to receive TCS and have the same risk of flare, risk of AEs and resource use as patients treated with placebo + TCS. The average treatment length in the model is 69 weeks.

Table 36: Information on dupilumab

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	Patients in the LIBERTY AD PRESCHOOL trial received a fixed dose based on body weight (200 mg every 4 weeks for patients ≥5 to 15 kg and 300 mg for patients ≥15 to <30 kg)	[redacted]	Based on weight and the same dosing regimen as in LIBERTY AD PRESCHOOL. The share of patients with a body weight below 15 kg might be different in the relevant Danish population
Length of treatment (time on treatment) (mean/median)	[redacted]	The average treatment length with dupilumab in the model is 69 weeks (i.e., 483 days). The maximum time on treatment in the model is 2 years	The clinical expert expects the average patient to be treated with dupilumab for approximately 2 years before the patient is stopped
Criteria for discontinuation	In the protocol for the LIBERTY AD PRESCHOOL trial, the following reasons for discontinuation were listed: • Anaphylactic reaction or other severe systemic reaction to the study drug • Diagnosis of a malignancy during study • Any infection that is opportunistic, such as active tuberculosis and other infections whose nature or course may suggest an immunocompromised status • Severe laboratory abnormalities: ◦ Neutrophil count ≤0.5 × 103 µL ◦ Platelet count ≤50 × 103 µL ◦ ALT and/or AST values greater than 3 × ULN with total bilirubin >2 × ULN (unless elevated bilirubin is related to confirmed Gilbert's Syndrome) ◦ Confirmed AST and/or ALT >5 × ULN (for more than 2 weeks) If the laboratory abnormality was considered causally related to study drug, study treatment was permanently discontinued. In cases in which a causal relationship to the study drug could be reasonably excluded (i.e., an alternative cause is evident), study treatment was discontinued, but it could be resumed when the laboratory abnormality was sufficiently normalised. A decision to resume study	Patients could only discontinue treatment with dupilumab in the model if they did not achieve EASI50 after 16 weeks in the model	According to the DDS guideline (60), patients >12 years will discontinue treatment in the Danish clinical setting if they do not achieve a response to the treatment defined as achieving EASI50 combined with a reduction of 4 points in DLQI after 16 weeks of treatment The clinical expert expects the criteria to be the same in children aged 6 months to 6 years According to the clinical expert, if patients experience severe conjunctivitis they will discontinue study treatment

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
	treatment should be made jointly by the investigator and medical monitor (medical monitor's written approval is required). • Treatment with any prohibited concomitant medication or procedure. The use of TCI and crisaborole was prohibited during the 2 weeks of TCS standardisation during part B of the trial (beginning on day -14 of the screening period) leading up the baseline visit and during the treatment period. The use of very high-potency or super-potent TCS was not allowed throughout the study (as their use is not recommended in patients under 12 years of age). However, medium- or high-potency TCS, TCIs, and crisaborole could be used as rescue treatment. In this situation, the study drug may be continued. Patients who received systemic corticosteroids or systemic non-steroid immunosuppressive drugs (e.g., cyclosporine, methotrexate, mycophenolate mofetil, azathioprine etc.) as rescue medication during part B of the study were permanently discontinued from the study drug		
Dupilumab's position in Danish clinical practice	-	After optimal topical treatment and before systemic therapy	After optimal topical treatment and before systemic therapy

8.2.2.3 Comparator

The comparator was placebo in combination with TCS and therefore, the comparator will not be further described in this section.

8.2.2.4 Relative efficacy outcomes

No efficacy outcomes were incorporated into the model; thus, the headings in this section related to efficacy have been deleted. AE outcomes were included in the model, which will be described in the following.

8.2.2.5 Adverse reaction outcomes

Adverse reaction outcomes in the clinical documentation submitted

The AEs experienced by patients with severe AD in the LIBERTY AD PRESCHOOL trial are presented in **Error! Reference source not found.**.

Adverse reaction outcomes in the health economic analysis submitted

The clinical expert was asked if the AEs presented in **Error! Reference source not found.** is representable of the AEs that are observed in the Danish clinical practice. The clinical expert found the AEs to be representative. The clinical expert was also asked which of the AEs in the table typically require treatment and how each of these AEs is managed. According to the clinical expert, conjunctivitis, molluscum contagiosum and impetigo typically require treatment, which consists of an additional consultation at the outpatient clinic. The share of patients who experienced conjunctivitis, molluscum contagiosum and impetigo, respectively, in the LIBERTY AD PRESCHOOL trial were used in the model and presented in Table 37.

Table 37: Adverse reaction outcomes from the LIBERTY AD PRESCHOOL trial and used in the model (data on file)

	Dupilumab	Placebo
Conjunctivitis		
First 16 weeks	[redacted]	[redacted]
Molluscum contagiosum		
First 16 weeks	[redacted]	[redacted]
Impetigo		
First 16 weeks	[redacted]	[redacted]

8.3 Extrapolation of relative efficacy

Not applicable.

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

Not applicable.

8.5 Resource use and costs

All costs related to the treatment of severe AD in children aged 6 months to <6 years were included in the cost model. To estimate the resource use and identify unit costs, data from the LIBERTY AD PRESCHOOL trial, the SPC on dupilumab, input from the Danish clinical expert and assumptions were applied. In the following, descriptions of each cost element and how the element was valued in the health economic analysis are presented.

8.5.1 Drug costs

All drug costs included in the model were based on the pharmacy purchasing price (PPP) obtained in February 2023. The dupilumab dose depends on body weight, and patients below 15 kg should receive 200 mg every 4 weeks, while patients with a body weight above 15 kg should receive 300 mg every 4 weeks. The PPP of the available packages of dupilumab is presented in Table 38.

Table 38: Applied dupilumab drug costs in the model

Product name	Active ingredient	Pack size	Strength	PPP (DKK)	Source/Note
Dupixent®	Dupilumab	2 vials	200 mg	8,195	Medicinpriser.dk (February 2023)
Dupixent®	Dupilumab	2 vials	300 mg	8,677	Medicinpriser.dk (February 2023)

In the LIBERTY AD PRESCHOOL trial, both patients randomised to the dupilumab group and the placebo group received the randomised treatment in combination with low-potency TCS. Medium- and high-potency TCS could be administered as rescue treatment in the trial. The average weekly doses in both arms are presented in Table 39. The mean weekly dose of TCS was higher for placebo than dupilumab. Especially, the lower use of medium/high potency TCS in patients treated with dupilumab is beneficial due to the safety concerns related to the long-term use of TCS in infants.

To estimate the drug cost of TCS, the TCS most frequently sold (mild, medium and high potency) was identified in the Danish Register of Pharmaceutical Sales (76). D07AA02 Hydrocortisone, D07AB02 Hydrocortisone butyrate and D07AC13 Mometason were the most frequently sold mild-, medium- and high-potency products in the Register of Pharmaceutical Sales, respectively. The package with the lowest price per gram was identified on the web page medicinpriser.dk and used in the model (see Table 40). In the model, the weekly dose of medium/high potency TCS was equally split between medium potency and high potency TCS.
No additional drug costs were included for placebo.

Table 39: Mean weekly dose of TCS, grams per week. Source: CSR data on file.

Product name	Low potency	Medium/high potency	Source/Note
Dupilumab	[redacted]	[redacted]	Post-hoc analysis, the LIBERTY AD PRESCHOOL trial
Placebo	[redacted]	[redacted]	Post-hoc analysis, the LIBERTY AD PRESCHOOL trial

Table 40: Applied TCS drug costs in the model

Product name	Active ingredient	Package size	PPP (DKK)	Unit cost per g used in model (DKK)	Source/Note
Mildison Lipid (Low potency)	Hydrocortisone	100 g	105.61	1.06	Medicinpriser.dk (February 2023)
Locoid (Medium potency)	Hydrocortisone butyrate	30 g	35.12	1.17	Medicinpriser.dk (February 2023)
Elocon (High potency)	Mometason	100 g	122.55	1.23	Medicinpriser.dk (February 2023)

8.5.2 Hospital costs

Dose administrations

The clinical expert informed that the first 2 doses of dupilumab are administered at the outpatient clinic at the hospital. Hereafter, most patients receive dupilumab treatment at home via self-administration. However, some patients or caregivers might not be comfortable with self-administration at home, and therefore, a small share of patients receive dupilumab at the hospital in the model. The clinical expert expects that 95% of patients can self-administer dupilumab at home after the first 2 doses, while 5% of patients will be administered at the hospital. A unit cost of DKK 1,618 was used for an outpatient visit where dupilumab is administrated. The unit cost was based on the 2023 DRG tariff 09MA99.

Table 41: Hospital cost related to dupilumab administration

	Input	Source
Share of patients who receive dupilumab at home after the 2 first administrations	95%	Clinical expert
Share of patients who continue to receive dupilumab at the outpatient clinic	5%	Clinical expert
Unit cost (DKK) of an outpatient visit where dupilumab is administrated	1,618	2023 DRG tariff 09MA99

Monitoring visits

Patients with severe AD who receive treatment should be monitored at the hospital. The clinical expert was consulted on how frequent patients should have monitoring visits at the hospital when on treatment with dupilumab and when on placebo treatment. According to the clinical expert, patients on dupilumab have 1-2 visits the first 16 weeks aside from the administration visits. Furthermore, patients have 3-4 visits the first year and 3 visits the following years. The clinical expert informed that 80% of the children treated with placebo + TCS would have a monitoring visit every second month, whereas 20% of the children would have a monitoring visit every month. This results in 7.2 visits per year on average. Therefore, patients on placebo have an average of 1.20 visits the first 16 weeks, 7.20 visits the first year (including the 1.20 visits the first 16 weeks) and 7.20 visits the following years. A unit cost of DKK 1,618 per monitoring visit was applied based on the 2023 DRG tariff 09MA99.

Table 42: Hospital visits related to monitoring visits

	Dupilumab	Placebo
First 16 weeks	1.5	1.20
First year (including the first 16 weeks)	3.5	7.20
Following years	3.0	7.20

The clinical expert was also consulted on how many blood tests patients get done. The clinical expert informed that patients do not get any routine blood tests done, and therefore, no costs for blood tests were included in the model. However, the model is flexible for the user to include costs for blood tests in the model.

Managing flares

Patients with AD can experience flares where their AD worsens. Flares require patients to visit the hospital to receive treatment. The clinical expert was consulted on how many patients that typically experience flares and how many

they typically experience on dupilumab and on placebo. [redacted] A unit cost of DKK 1,618 was used for an outpatient visit where flares are managed, as it was assumed that flares are managed at the outpatient clinic.

Table 43: Flare rate in the dupilumab arm and in the placebo arm

	Dupilumab	Placebo
First 16 weeks	[redacted]	[redacted]
First year	[redacted]	[redacted]
Following years	[redacted]	[redacted]

8.5.3 Cross-sectional costs

No cross-sectional costs were included in the model, as the clinical expert informed that there is no cross-sectional resource use related to the treatment of the patient population within the indication of interest. However, the model is flexible for the user to include visits to the general practitioner (GP). A unit cost of a GP consultation of DKK 153.61 was included in the model from 'Praktiserende lægers honorartabel, 0101 Konsultation, 2023'.

8.5.4 Costs of managing adverse events

Costs of managing AEs were included in the model. The clinical expert was consulted on which of the AEs observed in the LIBERTY AD PRESCHOOL trial that are expected in a Danish clinical setting and which AEs require treatment. The AEs observed in the subgroup of patients with severe AD are presented in **Error! Reference source not found.**. The clinical expert also provided insights on how the AEs are managed. According to the clinical expert, conjunctivitis, molluscum contagiosum and impetigo require treatment, and all patients (100%) who experience these AEs will receive treatment. Treatment of conjunctivitis is located at the outpatient clinic or in more severe cases at the Department of Ophthalmology. The treatment typically consists of lubricating eye drops, eye drops with steroids or another type of immune suppressive eye drops. Treatment of molluscum contagiosum is also located at the outpatient clinic but the AE can also be managed at home. According to the expert, home treatment consists of potassium hydroxide and at the outpatient clinic, patients can receive liquid nitrogen, curettage or cantharidin brushings. Impetigo treatment depends on the location of the AE and local or limited impetigo are treated with localised chlorhexidine wash or chlorhexidine cream. Bullous impetigo or widespread impetigo are typically treated with systemic antibiotics. Impetigo treatment is managed at the outpatient clinic.

As stated above, management of all three treatment requiring AEs consists of a consultation at the outpatient clinic. Therefore, the cost of managing AEs was based on the DRG 2023 tariff 09MA99 of DKK 1,618. The cost of AEs not requiring additional treatment is DKK 0 in the model. Based on discontinuation in the LIBERTY AD PRESCHOOL trial, it was not assumed that patients would discontinue treatment due to these AEs, as patients did not discontinue in the LIBERTY AD PRESCHOOL trial due to AEs.

Table 44 presents the share of patients who experience each treatment requiring AE in the model in the first 16 weeks, the first year and the following years. AEs in the first 16 weeks were from LIBERTY AD PRESCHOOL, and the

rates for the first year and the following years were calculated based on the rate for the first 16 weeks, as it was assumed that the risks were continued during all treatment years. The full list of AEs from LIBERTY AD PRESCHOOL is presented in Table 33.

Table 44: Treatment requiring AEs included in the model and share of patients who experience each AE. Source: CSR data on file.

	Dupilumab	Placebo
Conjunctivitis		
First 16 weeks	[redacted]	[redacted]
First year	[redacted]	[redacted]
Following years	[redacted]	[redacted]
Molluscum contagiosum		
First 16 weeks	[redacted]	[redacted]
First year	[redacted]	[redacted]
Following years	[redacted]	[redacted]
Impetigo		
First 16 weeks	[redacted]	[redacted]
First year	[redacted]	[redacted]
Following years	[redacted]	[redacted]

8.5.5 Patient and transportation costs

In accordance with DMC guidelines (67), patient-related and caregiver-related costs and transportation costs were included in the model. The patient and caregiver costs associated with dupilumab and placebo were based on the time spent on treatment-related activities and traveling back and forth from, e.g., visits to the hospital. Based on the DMC guidelines (67), a cost of DKK 181 per patient hour for both children and caregivers was applied. Transportation costs were also included. A distance of 20 km to and from the hospital (40 km in total per visit) was assumed, and a unit cost per km of DKK 3.51 was applied in accordance with DMC guidelines (67). Thus, a transportation cost of DKK 140 was applied for each hospital visit. It was assumed that patients spend 30 minutes on transportation to and from the hospital, i.e., 60 minutes per visit.

The patient and caregiver time spent on treatment-related activities was discussed with the clinical expert (see Table 45). For the drug administration at an outpatient visit, 35 minutes were included for the administration and 60 minutes of transportation, i.e., 1.58 hours of patient and caregiver time in total. For outpatient monitoring visits, 15 minutes were included for the consultation and 60 minutes for transportation per visit, i.e., 1.25 hours of patient and caregiver time in total. The visits where patients who experience a flare or one of the three included AEs (conjunctivitis, molluscum contagiosum and impetigo) receive treatment for the flare or the AEs were assumed to last the same amount of time as the monitoring visits (1.25 hours). Since no blood tests or visits to the GP were included in the model, no patient and caregiver time was included for these activities.

Table 45: Patient and caregiver time associated with treatment-related activities

	Dupilumab	Note	Source
Outpatient drug administration	1.58	35 minutes for the administration and 60 minutes of transportation	Clinical expert
Outpatient monitoring	1.25	15 minutes for the consultation and 60 minutes of transportation	Clinical expert
Outpatient treatment of flares	1.25	Assumed to be the same as for a monitoring visit	Assumption
Blood test	0	No time included, as no patients have blood tests	Clinical expert
GP visit	0	No time included, as no patients have GP visits	Clinical expert
Outpatient treatment of conjunctivitis	1.25	Assumed to be the same as for a monitoring visit	Assumption
Outpatient treatment of molluscum contagiosum	1.25	Assumed to be the same as for a monitoring visit	Assumption
Outpatient treatment of impetigo	1.25	Assumed to be the same as for a monitoring visit	Assumption

8.6 Results

8.6.1 Base case overview

Table 46 provides an overview of the settings applied in the base case of the health economic analysis.

Table 46: Base case overview

Intervention	Dupilumab + TCS
Comparator	Placebo + TCS
Type of model	Cost model
Time horizon	2 years (24 months)
Included costs	Drug costs (dupilumab and TCS) Hospital costs (drug administration, monitoring and flare treatment) Costs of managing adverse events Patient and caregiver costs Transportation costs
Dosage of pharmaceutical	Based on weight. Patients below 15 kg receive 200 mg, and patients above 15 kg receive 300 mg
Share below 15 kg	[redacted]
Share who self-administer dupilumab	[redacted]
Average time on treatment	Dupilumab: average of 69 weeks Placebo: 2 years
Drop-out rate at week 16	[redacted]

8.6.2 Base case results

This section presents the base case results of the cost analysis of dupilumab + TCS compared to placebo + TCS. The overall purpose of the cost analysis was to estimate the cost per patient for dupilumab relative to the current standard of care for patients with severe AD aged 6 months to <6 years. Results are presented over a time horizon of 2 years.

In the base case, the cost per patient for dupilumab was [redacted]

Table 47: Base case results

Per patient	Dupilumab	Placebo	Difference
Total costs	119,141	59,239	59,902

Per patient	Dupilumab	Placebo	Difference
Drug costs	74,421	2,456	71,965
Hospital costs	31,110	40,375	-9,265
Costs of managing AEs	1,381	1,188	192
Patient and caregiver time and transport costs	12,230	15,220	-2,990
Incremental results		59,902	

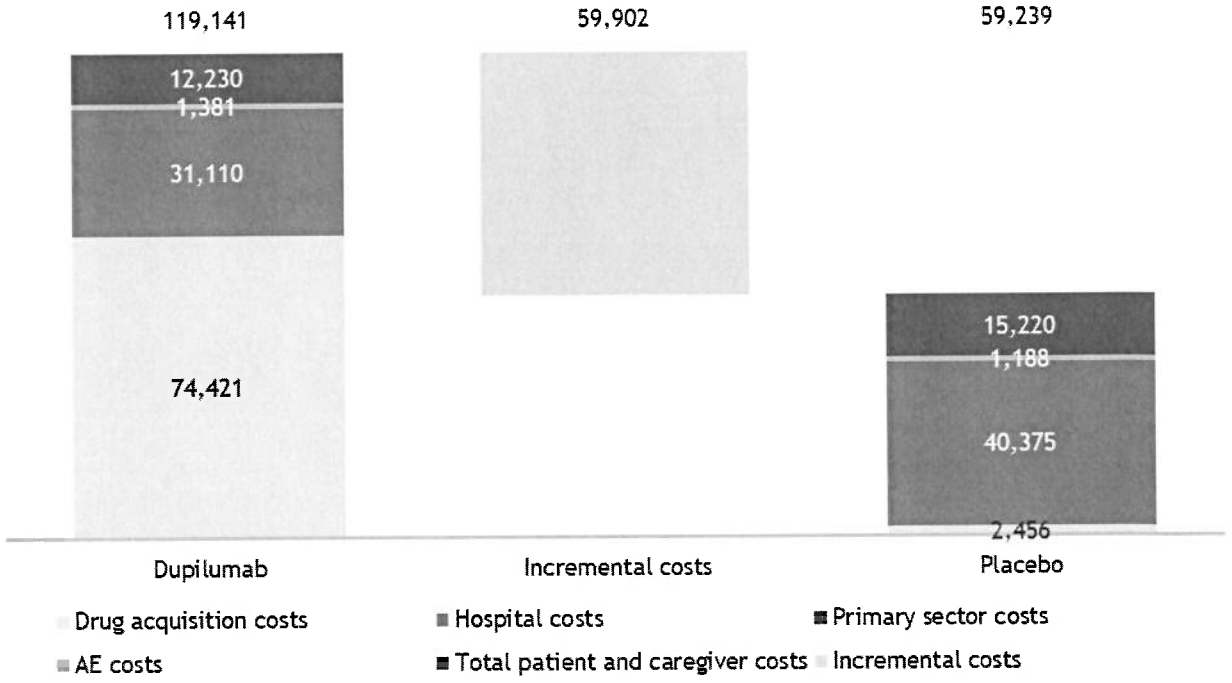


Figure 6: Result of the base case

8.7 Sensitivity analyses

Uncertainty in the input parameters in the cost model has been explored through various sensitivity analyses.

8.7.1 Deterministic sensitivity analyses

The DSAs included in the application and the rationale for including each DSA are presented in Table 48. In the DSAs included in the model, the point estimate was varied by +/- 20%. No scenario analyses were conducted.

According to the DMC guideline, scenario analyses on the time horizon should be presented. A scenario analysis using a time horizon of 1 year was performed; however, analyses with longer time horizons than 2 years were not preformed due to the fact that patients are included in the dupilumab indication for AD patients aged 6 years to 11 years once they turn 6, which is not included in the model.
It was discussed with the clinical expert how many patients in a Danish clinical setting achieve EASI50. The clinical expert expects that 65% of patients will achieve EASI50, which was achieved by 60.3% of patients in the LIBERTY AD PRESCHOOL trial. Due to the small difference between the estimate from the trial and the estimate from the clinical expert, we did not include these parameters in the DSA.

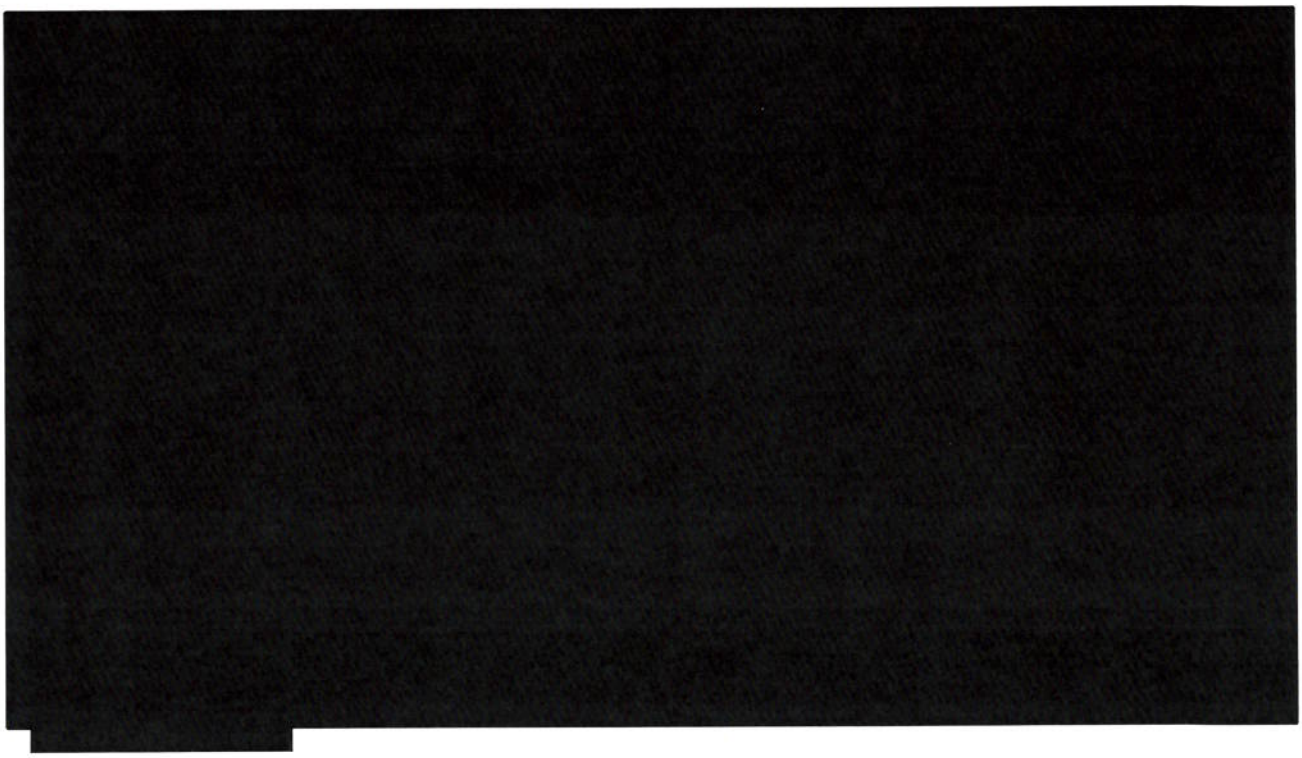
Results of the deterministic sensitivity analyses are presented in Table 48 and [redacted]. The PPP of dupilumab and the share of patients achieving EASI50 at week 16 impacts the incremental results the most. Changing the time horizon to 1 year resulted in a DKK 23,765 decrease in incremental costs to DKK 36,137.

Table 48: One-way sensitivity and scenario analyses results

	Change	Reason for including	Incremental cost (DKK)
Base case	-	-	59,902
Share of patients below 15 kg	[redacted]	[redacted]	[redacted]
EASI50 response	[redacted]	[redacted]	[redacted]
Dupilumab PPP 200 mg, DKK	[redacted]	[redacted]	[redacted]
Dupilumab PPP 300 mg, DKK	[redacted]	[redacted]	[redacted]
Dupilumab, unit cost of an outpatient drug administration visit, DKK	[redacted]	[redacted]	[redacted]
Dupilumab, number of outpatient visits, 16 weeks	[redacted]	[redacted]	[redacted]
Dupilumab, number of outpatient visits, first year	[redacted]		[redacted]

	Change	Reason for including	Incremental cost (DKK)
Dupilumab, number of outpatient visits, Following years			
Placebo, number of outpatient visits, 16 weeks			
Placebo, number of outpatient visits, first year			
Placebo, number of outpatient visits, following years			
Unit cost for outpatient monitoring visits, DKK			
Dupilumab, rate of flares, first year			
Dupilumab, rate of flares, following years			
Placebo, rate of flares, first year			
Placebo, rate of flares, following years			
Unit cost for outpatient treatment of flares, DKK			
Dupilumab, share of patients experiencing conjunctivitis, 16 weeks			
Dupilumab, share of patients experiencing molluscum contagiosum, 16 weeks			

	Change	Reason for including	Incremental cost (DKK)
Dupilumab, share of patients experiencing impetigo, 16 weeks			
Placebo, share of patients experiencing conjunctivitis, 16 weeks			
Placebo, share of patients experiencing molluscum contagiosum, 16 weeks			
Placebo, share of patients experiencing impetigo, 16 weeks			
Time horizon			



8.7.2 Probabilistic sensitivity analyses

Not applicable, since the only parameter in the model is costs.

9. Budget impact analysis

The purpose of the budget impact analysis (BIA) is to estimate the budgetary impact of recommending dupilumab as standard treatment for patients aged 6 months to <6 years with severe AD (IGA = 4). The budget impact is estimated per year in the first 5 years after the recommendation of dupilumab. The BIA compares the expenditures in the scenario where dupilumab is recommended as a possible standard treatment and the scenario where dupilumab is not recommended as a possible standard treatment. The total budget impact per year is the difference between the two scenarios. The expenditure per patient is equivalent to the cost per patient without patient, caregiver and transportation costs. A treatment length of 2 years (24 months) was applied in the budget impact analysis.

9.1 Number of patients

The clinical expert was consulted on the prevalence and incidence of children aged 6 months to <6 years with severe AD in Denmark. Sanofi expects a prevalence of between 50 and 80 patients and an incidence of 10 to 12 children each year are candidates for treatment with dupilumab. These estimates were validated by the clinical expert and based on this, we assumed a prevalence of 50 patients and an incidence of 11 new patients per year are candidates to be treated with dupilumab. According to the clinical expert, the development in the prevalence and incidence has been stable for at least the last 5 years.

In the first year of the BIA, the full prevalent population is expected to initiate treatment for 2 years. The following years, 11 patients will enter the model and initiate treatment for 2 years. It was assumed that 75% of the prevalent and incident patients, who are candidates to dupilumab, will be treated with dupilumab in case of recommendation. Taking learnings from diabetes treatment in children; It is expected that not all eligible patients will be treated due to hesitation and needle fear. Therefore, the market share in the scenario that dupilumab is recommended is 75% of the prevalent and incident patients. In the scenario where dupilumab is not recommended, it was assumed that the market share will be 0%. The number of patients expected to be treated are presented in Table 49 and Table 50 if dupilumab is introduced or if dupilumab is not introduced, respectively. The total number of patients treated in both scenarios are 50 in the first year (i.e., the prevent population), 61 in the second year (i.e., 50 prevalent patients starting treatment in year 1, and 11 incident patient starting treatment in year 2 of the BIA) and 22 patients in year 3 (i.e., 11 incident patients starting treatment in year 2 and 11 incident patients starting in year 3). Furthermore, 22 patients are treated in year 4 and 5.

Table 49: Number of patients expected to be treated over the next 5-year period – if dupilumab is introduced (rounded numbers)

	Year 1	Year 2	Year 3	Year 4	Year 5
Dupilumab	38	46	17	17	17
Placebo	13	15	6	6	6
Total number of patients	50	61	22	22	22

Table 50: Number of patients expected to be treated over the next 5-year period – if dupilumab is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Dupilumab	0	0	0	0	0
Placebo	50	61	22	22	22
Total number of patients	50	61	22	22	22

9.2 Expenditure per patient

In Table 51, we present the cost per patient for the first 5 years for a patient receiving dupilumab and a patient receiving placebo.

Table 51: Costs per patient per year (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
Dupilumab, costs per patient	59,342	49,255	0	0	0
Placebo, costs per patient	22,403	22,403	0	0	0

9.3 Budget impact results

An overview of the results of the budget impact analysis is presented in Table 52. The table shows the total costs of treatment per year in the case where dupilumab is recommend and in the case where dupilumab is not recommend as standard treatment. The budget impact of recommending dupilumab for use at the Danish hospitals is DKK 526,269 in year 5. Over all 5 years, the budget impact is DKK 4,275,687. It is important to note that the drug costs presented in Table 52 are based on PPPs. A graphic presentation of the results is presented in Figure 8.

Table 52: Expected budget impact of recommending dupilumab for the current indication (thousand DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
Dupilumab is recommended	2,505	2,678	1,019	1,019	1,019
Of which: Drug costs	1,560	1,649	630	630	630
Of which: Hospital costs	911	988	374	374	374
Of which: Adverse reaction costs	34	41	15	15	15
Minus: Dupilumab is NOT recommended	1,120	1,367	493	493	493
Of which: Drug costs	63	76	28	28	28
Of which: Hospital costs	**1,027**	**1,253**	**452**	**452**	**452**
Of which: Adverse reaction costs	**30**	**37**	**13**	**13**	**13**
Budget impact of the recommendation	**1,385**	**1,312**	**526**	**526**	**526**

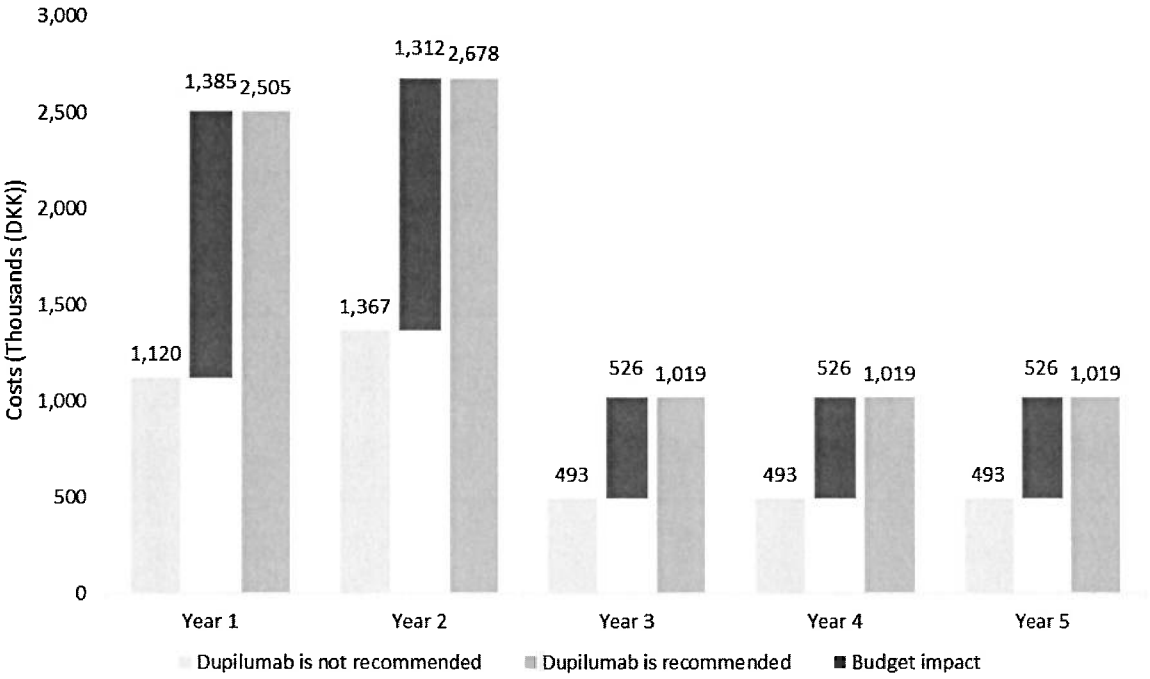


Figure 8: Budget impact of recommending dupilumab

9.4 Budget impact sensitivity

Sensitivity analyses were performed for the budget impact analysis to assess the uncertainty in the estimated budgetary impact on the Danish regions' budget. The performed sensitivity analyses are presented in Table 53.

Table 53: Sensitivity analyses performed in the budget impact analysis (thousand DKK)

	Year 1		Year 2		Year 3		Year 4		Year 5	
	-20%	+20%	-20%	+20%	-20%	+20%	-20%	+20%	-20%	+20%
Prevalence	1,108	1,662	1,110	1,513	526	526	526	526	526	526
Incidence	1,385	1,385	1,251	1,373	421	632	421	632	421	632

10. Discussion on the submitted documentation

Dupilumab is the first and only targeted therapy indicated for children aged 6 months to <6 years diagnosed with severe AD. In addition, dupilumab is the only biologic that inhibits both IL-4 and IL-13 signalling pathways, which are the key central drivers of AD and other type 2 inflammatory diseases. In Denmark, dupilumab has already been recommended for various other indications, such as severe AD in patients aged 6 years to 11 years, and adolescents and adults with moderate-to-severe AD. Furthermore, dupilumab is also indicated and recommended for the treatment of asthma and severe chronic rhinosinusitis with nasal polyposis. If recommended for children aged 6 months to <6 years, dupilumab will be the first and only recommended treatment with EMA indication for children aged 6 months to <6 years with severe AD in Denmark. Topical therapies are the mainstay of treatment for infants with AD; however, the long-term use in infants is limited due to safety concerns, as TCS is associated with a range of local adverse events, particularly at higher doses (3,33). Especially the risk of skin atrophy is a particular concern when treating thin-skin areas such as the face, neck, axillae, perineum, and intertriginous surfaces (where two skin areas may rub together). In rare cases, long-term TCS treatment can result in systemic adverse effects, such as hyperglycaemia, glaucoma, poor growth, hypertension, and adrenal insufficiency (3,61). Currently, the only treatment options available for children with severe AD who are not adequately controlled with topical therapies are off-label use of systemic immunosuppressants such as methotrexate, azathioprine, mycophenolate mofetil and cyclosporine A (60). In addition to the use of systemic immunosuppressants typically not being appropriate for the treatment of infants due to toxicity, the evidence for the long-term efficacy of the above-mentioned systemic therapies is limited, and the therapies are associated with safety concerns. The systemic immunosuppressants have been associated with serious adverse events such as infection, nephrotoxicity, pulmonary fibrosis, hepatic fibrosis and toxicity, bone marrow suppression, leucopenia, lymphoma and skin cancer (56,62–64).

AD is associated with a substantial humanistic burden and has major implications on the QoL for both children with AD and their caregivers and families. In the pivotal phase III trial comparing the efficacy and safety of dupilumab + TCS and placebo + TCS, the LIBERTY AD PRESCHOOL trial, patients treated with dupilumab + TCS experienced [redacted] in the extent and severity of skin lesions measured with EASI and SCORAD. The RR for EASI75 was [redacted]. Dupilumab also demonstrated [redacted] in patients' QoL measured with CDLQI (patients aged ≥4 years old) and IDQOL (patients aged <4 years old). In CDLQI, the LS mean difference in change from baseline was [redacted] in the dupilumab + TCS group compared to the placebo + TCS group after week 16, and [redacted] In IDQOL, the LS mean difference in change from baseline was [redacted] in the dupilumab + TCS group compared to the placebo + TCS group after week 16, and the difference was [redacted] In terms of safety, dupilumab + TCS also demonstrated a favourable and tolerable safety profile. Aside from the demonstrated efficacy of dupilumab, the drug also provides a convenient dosing regimen, as it is administered subcutaneously every 4 weeks, i.e., patients and caregivers can administer the treatment at home after having received the first 2 initial doses at the hospital.

The health economic analysis was a cost analysis of the costs related to treating children aged 6 months to <6 years with severe AD with dupilumab + TCS compared to placebo + TCS. A cost analysis approach was chosen over a cost-utility approach, as it was regarded as inappropriate to conduct a cost-utility analysis due to the complexity and uncertainties related to measuring HRQoL in children, especially very young children aged 6 months to <6 years. In addition, a cost analysis approach to the health economic analysis has been applied in all previous DMC evaluations of AD. The cost analysis resulted in an incremental cost of DKK 59,902 between dupilumab + TCS and placebo + TCS over a time horizon of 2 years. The budget impact of recommending dupilumab for children aged 6 months to <6 years with severe AD was DKK 526,269 5 years after the recommendation.

Most of the input values applied in the model were informed by the LIBERTY AD PRESCHOOL trial or came from the clinical expert. Alternative values of the inputs in the model were assessed in the DSA to assess the impact on the result of the health economic analysis if alternative values for these inputs were applied. No Danish treatment guideline exists for severe AD in children aged 6 months to <6 years, and therefore, it is currently not determined how complete response and partial response should be defined for patients aged 6 months to <6 years. The clinical expert expects that complete and partial response will be defined in the same way as for the other age groups as achieving EASI75 and EASI50 combined with a reduction of 4 points on the DLQI (in this case CDLQI or IDQOL), respectively. The definition of partial response is different in the DDS guideline, where partial response is defined as achieving EASI50 with the need for a 4-point reduction in DLQI. This introduces uncertainty to the drop-out rate applied in the model, as the proportion of patients who do not achieve EASI50 in Danish clinical practice might be different from the trial due to this difference in the definitions (39.7% do not achieve EASI50 in the trial and drop out at week 16 in the model).

11. List of experts

The clinical expert consulted in the preparation of this application is Anne Birgitte Nørremark Simonsen, Clinical Associate Professor, Department of Clinical Medicine, Hellerup

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

The efficacy and safety of dupilumab have been assessed in the LIBERTY AD PRESCHOOL trial (66). LIBERTY AD PRESCHOOL is a randomised, double-blind, placebo-controlled, parallel-group, phase 3 trial of dupilumab in combination with TCS compared to placebo in combination with TCS in patients aged 6 months to younger than 6 years with moderate-to-severe AD. Since the LIBERTY AD PRESCHOOL trial is a head-to-head trial of dupilumab and placebo, no literature search was conducted in accordance with the DMC method guideline (67). Based on this, the headings in this section have been deleted.

Appendix B Main characteristics of included studies

Table 54: Main characteristics of the LIBERTY AD PRESCHOOL trial. Source: Paller et al. 2022 (66) and CSR data on file.

Trial Name: Safety, Pharmacokinetics and Efficacy of Dupilumab in Patients ≥6 Months to <6 Years With Moderate-to-Severe Atopic Dermatitis (LIBERTY AD PRESCHOOL) (Liberty AD) Part B	NCT number: NCT03346434
Objective	• Primary objective is to demonstrate the efficacy of multiple doses of dupilumab over 16 weeks of treatment when administered concomitantly with TCS in paediatric participants, 6 months to less than 6 years of age, with moderate-to-severe AD. • Secondary objective is to assess the safety and immunogenicity of multiple doses of dupilumab over 16 weeks of treatment when administered concomitantly with TCS in participants 6 months to less than 6 years of age with moderate-to-severe AD.
Publications – title, author, journal, year	Efficacy and safety of dupilumab in children aged ≥6 months to <6 years with moderate-to-severe atopic dermatitis, Paller et al., British Journal of Dermatology, 2022 (49)
Study type and design	Randomised, double-blind, parallel-group, placebo-controlled phase 3 study

Sample size (n)

	Placebo + TCS (N = 79)	Dupilumab 200/300 mg Q4W + TCS (N = 83)	Total (N = 162
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
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Trial Name: Safety, Pharmacokinetics and Efficacy of Dupilumab in Patients ≥6 Months to <6 Years With Moderate-to-Severe Atopic Dermatitis (LIBERTY AD PRESCHOOL) (Liberty AD) Part B	NCT number: NCT03346434				
	[redacted]				

Trial Name: Safety, Pharmacokinetics and Efficacy of Dupilumab in Patients ≥6 Months to <6 Years With Moderate-to-Severe Atopic Dermatitis (LIBERTY AD PRESCHOOL) (Liberty AD) Part B	NCT number: NCT03346434

Main inclusion and exclusion criteria

Key inclusion criteria

- Diagnosis of AD according to the American Academy of Dermatology consensus criteria at the screening visit
- Participants with documented recent history (within 6 months before the screening visit) of inadequate response to topical AD medication(s)
- IGA score at screening and baseline visits
  - part A: IGA = 4
  - part B: IGA ≥3
- EASI score at screening and baseline visits
  - part A: EASI ≥21
  - part B: EASI ≥16
- Body Surface Area (BSA) involvement at screening and baseline visits
  - part A: ≥15%
  - part B: ≥10%
- At least 11 (of a total of 14) applications of a topical emollient (moisturiser) during the 7 consecutive days immediately before the baseline visit (not including the day of randomisation) (for part B of the study only)
- Baseline worst scratch/itch score weekly average score for maximum scratch/itch intensity ≥4 (for part B of the study only)
- At least 11 (of a total of 14) daily applications of low potency TCS during the 2-week TCS standardisation period (beginning on day -14) leading up to the baseline visit (for part B of the study only)

Key exclusion criteria

- Prior treatment with dupilumab
- History of important side effects of low potency TCS (only applicable for part B of the study)
- Having used immunosuppressive/immunomodulating drugs within 4 weeks before the baseline visit
- Treatment with a live (attenuated) vaccine within 4 weeks before the baseline visit
- Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiprotozoals, or antifungals within 2 weeks before the baseline visit
- Known or suspected immunodeficiency, known history of human immunodeficiency virus (HIV) infection or HIV seropositivity at the screening visit, established diagnosis of HBV infection or HBV seropositivity at screening, established diagnosis of HCV infection or HCV seropositivity at screening
- History of malignancy at any time before the baseline visit
- Diagnosed active endoparasitic infections or at high risk of these infections
- Severe concomitant illness(es) that, in the investigator's judgment, would adversely affect the patient's participation in the study
- Body weight <5 kg or ≥30 kg at baseline (only applicable part B of the study)

Trial Name: Safety, Pharmacokinetics and Efficacy of Dupilumab in Patients ≥6 Months to <6 Years With Moderate-to-Severe Atopic Dermatitis (LIBERTY AD PRESCHOOL) (Liberty AD) Part B	NCT number: NCT03346434
Intervention	**Dupilumab 200 mg or 300 mg Q4W + TCS** Participants with baseline weight of ≥5 to <15 kg received subcutaneous injections of 200 mg or participants with baseline weight ≥15 to <30 kg received subcutaneous injections of 300 mg of dupilumab at Day 1 and Q4W from week 4 to week 12. Participants applied low-potency TCS once daily to areas with active lesions for 16 weeks.
Comparator(s)	**Placebo + TCS** Participants received subcutaneous injection of placebo matched to dupilumab Q4W for 16 weeks along with low potency TCS applied once daily to areas with active lesions.
Follow-up time	Screening of up to 56 days, including TCS standardisation period of 2 weeks. Treatment period of 16 weeks, and follow-up of 12 weeks (for patients who do not enter the OLE study). Starting on day -14, all patients will be required to initiate treatment with low-potency TCS using a standardised regimen. During the treatment period, patients will have in-clinic visits at baseline, week 1, week 2 and week 4, then monthly in-clinic visits through week 16 with weekly telephone visits in between the clinic visits. Safety and laboratory assessments, samples for dupilumab concentration and response to dupilumab, and efficacy assessments will be performed or collected at specified time points throughout Part B of the study. The end of treatment period visit will occur at week 16, 4 weeks after the last dose of study drug. The primary endpoint will be assessed at this visit. An OLE study in patients aged 6 months to <18 years old is currently ongoing. Patients who complete the treatment period in Part B may subsequently be eligible to participate in the OLE study. Patients who decline to participate in the OLE will enter a follow-up period of 12 weeks. Follow-up visits will occur every 4 weeks from week 20 through week 28. During the follow-up period, patients will be monitored for safety and tolerability and have laboratory and clinical assessments.
Is the study used in the health economic model?	No

Primary, secondary and exploratory endpoints	**Primary endpoint:**
	• Percentage of Participants With IGA Score 0 or 1 at Week 16 [Time Frame: Week 16]
	  o The IGA is an assessment scale used in clinical studies to rate the severity of AD globally, based on a 5-point scale ranging from 0 to 4 where 0 = clear; 1=almost clear; 2=mild; 3=moderate; 4=severe. A negative change from baseline indicated improvement. Percentage of participants with IGA score of '0' or '1' is reported.
	• Percentage of Participants With EASI-75 (≥75% Improvement From Baseline) at Week 16 [Time Frame: Week 16]
	  o The EASI score is used to measure the severity and extent of AD and measured erythema, infiltration, excoriation and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores indicating the worse severity of AD. EASI-75 responders were the participants who achieved ≥75% overall improvement in EASI score from baseline at Week 16.
	Secondary endpoint:

- Number of Participants With at Least One SAE Through Week 16 [Time Frame: Baseline through Week 16]
- Number of Participants With at Least One Skin Infection TEAE (excluding herpetic infection) Through Week 16 [Time Frame: Baseline through Week 16]
- Number of Participants With at Least One Positive Treatment-Emergent ADA [Time Frame: Baseline up to Day 197]
    - Treatment emergent: Post-dose positive result when baseline results were negative.
- Percent Change From Baseline in EASI Score at Week 16 [Time Frame: Week 16]
    - The EASI score is used to measure the severity and extent of AD and measures erythema, infiltration, excoriation, and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores indicating the worse severity of AD. A negative change from baseline indicated improvement.
- Percent Change From Baseline in Weekly Average of Daily Worst Scratch/Itch/NRS at Week 16 [Time Frame: Week 16]
    - Pruritus NRS is an assessment tool used to report intensity of participant's pruritus (itch), both average and maximum intensity, during a 24-hr recall period. Participants were asked two questions: 1) For average itch intensity: how would you rate your itch overall (on average) during the previous 24 hours; 2) For maximum itch intensity: How would you rate your itch at the worst moment during the previous 24 hours? Both questions were rated on a scale: 0-10 with 0=no itch & 10=worst itch imaginable. A negative change from baseline indicated improvement.
- Percentage of Participants With Improvement (Reduction From Baseline) of Weekly Average of Daily Worst Scratch/Itch/NRS ≥4 Points at Week 16 [Time Frame: Week 16]
    - Pruritus NRS is an assessment tool used to report intensity of subject's pruritus (itch), both average and maximum intensity, during a 24-hr recall period. Subjects were asked two questions: 1) For average itch intensity: how would you rate your itch overall (on average) during the previous 24 hours; & 2) For maximum itch intensity: How would you rate your itch at the worst moment during the previous 24 hours? Both questions were rated on a scale: 0-10 with 0=no itch & 10=worst itch imaginable.
- Percentage of Participants With Improvement (Reduction From Baseline) of Weekly Average of Daily Worst Scratch/Itch/NRS ≥3 Points at Week 16 [Time Frame: Week 16]
    - Pruritus NRS is an assessment tool used to report intensity of participant's pruritus (itch), both average and maximum intensity, during a 24-hr recall period. Participants were asked two questions: 1) For average itch intensity: how would you rate your itch overall (on average) during the previous 24 hours; & 2) For maximum itch intensity: How would you rate your itch at the worst moment during the previous 24 hours? Both questions were rated on a scale: 0-10 with 0=no itch & 10=worst itch imaginable.
- Percentage of Participants Who Achieved EASI-50 (≥50% Improvement From Baseline) at Week 16 [Time Frame: Week 16]
    - The EASI score is used to measure the severity and extent of AD and measured erythema, infiltration, excoriation, and lichenification on 4 anatomic regions of the

body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores indicating the worse severity of AD. EASI-50 responders were the participants who achieved ≥50% overall improvement in EASI score from baseline at week 16.

- Percentage of Participants Who Achieved EASI-90 (≥90% Improvement From Baseline) at Week 16 [Time Frame: Week 16]
    - The EASI score is used to measure the severity and extent of AD and measured erythema, infiltration, excoriation, and lichenification on 4 anatomic regions of the body: head, trunk, upper and lower extremities. The total EASI score ranges from 0 (minimum) to 72 (maximum) points, with the higher scores indicating the worse severity of AD. EASI-90 responders were the participant who achieved ≥90% overall improvement in EASI score from baseline at week 16.
- Change From Baseline in Percent BSA Affected by AD at Week 16 [Time Frame: Week 16]
    - BSA affected by AD was assessed for each section of the body (the possible highest score for each region was: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]). It was reported as a percentage of all major body sections combined. A negative change from baseline indicated improvement.
- Change From Baseline in POEM at Week 16 [Time Frame: Week 16]
    - The POEM is a 7-item questionnaire that assesses disease symptoms (dryness, itching, flaking, cracking, sleep loss, bleeding and weeping) with a scoring system of 0 (absent disease) to 28 (severe disease) (high score indicative of poor quality of life [QOL]). A negative change from baseline indicated improvement.
- Percent Change From Baseline in SCORAD at Week 16 [Time Frame: Week 16]
    - The SCORAD index is a clinical tool for assessing the severity of AD. Extent and intensity of eczema as well as subjective signs (insomnia etc.) are assessed and scored. Total score ranges from 0 (absent disease) to 103 (severe disease). A negative change from baseline indicated improvement.
- Change From Baseline in Participant's Sleep Quality NRS at Week 16 [Time Frame: Week 16]
    - A sleep diary is completed by the parent/caregiver and included 2 questions assessing the caregiver's sleep and 6 questions assessing the child's sleep based on caregiver observation. Sleep diary items, either alone or in combination, serve as subjective measures of sleep quality, difficulty falling asleep, night-time awakenings and sleep duration. Sleep quality is measured using an 11-point NRS (0 to 10) in which 0 indicates worst possible sleep, while 10 indicates best possible sleep.
- Change From Baseline in Participant's Skin Pain NRS at Week 16 [Time Frame: Week 16]
    - Skin pain was assessed by the parent/caregiver and measured using a 11-point scale (0 to 10) in which 0 indicated no pain, while 10 indicated worst pain possible. A negative change from baseline indicated improvement.
- Change From Baseline in Dermatitis Family Index (DFI) at Week 16 [Time Frame: Week 16]
    - DFI is a 10-item questionnaire with items inquiring about housework, food preparation, sleep, family leisure activity, shopping, expenditure, tiredness, emotional distress, relationships, and impact of helping with treatment on the primary caregiver's life. DFI

questions were scored on a 4-point Likert scale ranging from 0 to 3, so that the total DFI score ranges from 0 to 30. The time frame of reference was the past week. A higher DFI score indicated greater impairment in family quality of life (QOL) as affected by atopic dermatitis. A negative change from baseline indicated improvement.

- Change From Baseline in CDLQI at Week 16 [Time Frame: Week 16]
    - CDLQI is a validated 10 question tool to measure impact of skin disease on QOL in children by assessing how much the skin problem has affected the subjects over past week. Nine questions were scored as follows: Very much = 3, Quite a lot = 2, Only a little = 1, Not at all or unanswered = 0. Question 7 has an added possible response, which was scored as 3. CDLQI equals the sum of the score of each question (max. = 30, min. = 0). Higher the score, the greater the impact on QOL. A negative change from baseline indicated improvement.
- Change From Baseline in IDQOL at Week 16 [Time Frame: Week 16]
    - IDQOL is used to evaluate quality of life for subjects of less than 4 years of age. IDQOL questionnaires were designed for infants (below the age of 4 years) with atopic dermatitis. The IDQOL was calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score in each questionnaire, the more quality of life is impaired. A negative change from baseline indicated improvement.
- Percentage of TCS Medication-free Days From Baseline to Week 16 [Time Frame: Baseline up to Week 16]
    - Percentage of TCS medication-free days was calculated as the number of days that a subject used neither TCS/TCI nor system rescue therapy divided by the study days.
- Mean Weekly Dose of Low Potency TCS in Grams From Baseline to Week 16 [Time Frame: Baseline up to Week 16]
    - Mean weekly dose of TCS in grams/week for low-potency TCS from baseline to Week 16 is reported.
- Mean Weekly Dose of TCS in Grams for Medium or High Potency TCS From Baseline to Week 16 [Time Frame: Baseline up to Week 16]
    - Mean weekly dose of TCS in grams/week for medium- or high-potency TCS from baseline to Week 16 is reported.
- Mean Number of Caregiver Missed Work Days Through Week 16 [Time Frame: Baseline through Week 16]
    - Mean of number of caregiver missed work days through Week 16 is reported.

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Method of analysis	A sample size of 160 patients (80 per treatment group), at the two-sided 5% significance level, was estimated to provide 88% power to detect a difference of 21% between treatment groups in the proportion of patients with IGA 0 or 1 at week 16, assuming a response rate of 33% for the dupilumab group and 11% for the placebo group; and 99% power to detect a 43% difference in the proportion of patients with EASI-75 at week 16, assuming response rates of 70% for the dupilumab group and 27% for the placebo group. Assumptions for power calculations were based on the LIBERTY AD PEDS phase 3 trial in children aged 6–11 years (NCT03345914). Categorical endpoints were analysed using a Cochran-Mantel-Haenszel test after adjustment for randomisation strata. Proportions of patients with a categorical endpoint are presented as model-derived estimates. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, AEs or lack of efficacy (as deemed by the investigator) were considered non-responders. Missing data due to any other reason, including COVID-19, were imputed using multiple imputation (66). Continuous endpoints were analysed using analysis of covariance, with treatment group, stratification factors, and relevant baseline measurements included in the model. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, AEs or lack of efficacy (as deemed by the investigator) were imputed by WOCF. Missing values due to other reasons were handled by multiple imputation. A hierarchical procedure was used to control the overall type 1 error rate at 0.05 for the primary and secondary endpoints for dupilumab versus placebo. Each hypothesis was formally tested only if the preceding one was significant at the two-sided 0.05 significance level (66). The primary efficacy analyses were conducted using the FAS, which included all randomly assigned patients based on the treatment allocated (as randomly assigned). Prespecified sensitivity analyses were performed for primary and coprimary endpoints, key secondary endpoints, and the proportion of patients with 4-point or greater improvement in worst itch and scratch NRS score using all observed values regardless of rescue treatment use and last observation carried forward analysis. P-values for comparisons not in the hierarchy are nominal. All statistics for safety, biomarkers and pharmacokinetics were descriptive. Safety analyses were conducted using the safety analysis set, which included all randomly assigned patients who received any study drug, as treated. If a patient was randomly assigned and did not receive any study treatment, they were not included in the SAF. Biomarker analyses were conducted using the FAS. The pharmacokinetics analysis population included all patients who received any study drug and who had at least one non-missing result following the first dose of study drug. Statistical analyses were performed using SAS version 9.4 or higher (66).
Subgroup analyses	Currently no planned subgroup analysis
Other relevant information	No

Appendix C Baseline characteristics of patients in LIBERTY AD PRESCHOOL used for the comparative analysis of efficacy and safety

In the following, we present the baseline characteristics of the patient population from the LIBERTY AD PRESCHOOL trial with severe AD and compare these patients to the Danish patient population within the dupilumab indication relevant for this application.

Table 55: Baseline characteristics of patients included in the LIBERTY AD PRESCHOOL trial with severe AD (IGA = 4). Source: CSR data on file.

	LIBERTY AD PRESCHOOL	
	Dupilumab + TCS (n = 63)	Placebo + TCS (n = 62)
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Comparability of patients across studies

Not relevant, as only one study is included.

Comparability of the study populations with Danish patients eligible for treatment

The comparability of the study population with Danish patients within the dupilumab indication was discussed with the clinical expert. The expert informed that the Danish patients have characteristics similar to the patient population in the LIBERTY AD PRESCHOOL, i.e., the populations are comparable.

Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

Table 56: Definition, validity and clinical relevance of included outcomes

Outcome measure	Definition	Validity	Clinical relevance
Proportion of patients who achieve at least 75% eczema reduction on the EASI scale	Defined as ≥75% improvement from baseline. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, AEs and lack of efficacy were considered non-responders. Patients with missing values of EASI score due to other reasons, including COVID-19, were imputed by MI, and the response status was then derived	The validity and reliability of the EASI has been examined in several studies (77–80)	EASI is a clinically relevant outcome and a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (77). The outcome has also been used in previous DMC evaluations of AD. The DMC has in previous evaluations of dupilumab (for children aged ≥6 years) regarded a difference of 10 percentage points between groups to be the minimum clinically important difference (MCID) for EASI-75 (81). An MCID for EASI-75 for infants and children <6 years has not been established
Mean reduction in EASI from baseline to week 16	See above	See above	See above. Schram et al. 2012 have presented a MCID for the mean change from baseline in EASI of 6.6 points (78). No MCID for infants and children <6 years has been established for this outcome
Proportion of patients who achieve at least a 50% eczema reduction on the SCORAD scale	Defined as >=50% reduction in SCORAD from baseline response at week 16. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, AEs and lack of efficacy were considered non-responders. Patients with missing values of SCORAD score due to other reasons, including COVID-19,	The SCORAD is a validated tool used in clinical research and clinical practice that was developed to standardise the evaluation of the extent and severity of AD (42)	SCORAD is a clinically relevant outcome often used in clinical research and clinical practice that was developed to standardise the evaluation of the extent and severity of AD (42). The outcome has also been used in previous DMC evaluations of AD. The DMC has

Outcome measure	Definition	Validity	Clinical relevance
	were imputed by MI, and the response status was then derived. All non-missing data were used for MI. In MI, the seed numbers were 12345 and 54321 with imputation size 40		in a previous evaluation of dupilumab (12-17 year old) stated that a difference of 17.5 percentage points in SCORAD-50 would be clinically relevant for the patient (82). A MCID in SCORAD-50 has not been established for infants and children <6 years of age
Proportion of patients who achieve an improvement of at least 3 points in POEM	The POEM consists of 7 items that evaluate the frequency of 7 symptoms (itch, sleep disturbance, dryness, flaking, weeping or oozing, bleeding and cracking) in the past 7 days, and the scores range from 0 to 28 (71). In children, it is the caregiver's response that the 7 items are assessed. All of the 7 items carry equal weight and are scored from 0 to 4, i.e., a 5-point scale is used where 0 is no days, 1 is 1 to 2 days, 2 is 3 to 4 days, 3 is 5 to 6 days, and 4 is every day. A high score is indicative of poor QoL	The POEM has been validated in Charman et al. 2004 (70)	POEM is recommended by HOME and is a 7-item and well-validated questionnaire used in clinical practice and clinical trials to assess disease symptoms in children and adults with atopic eczema (70). Gaunt et al. 2016 have presented a MCID for POEM in young children (up to 5 years of age) to be 3 points (83). In a previous DMC evaluation of dupilumab, a MCID of 10 percentage points in the proportion of patients who achieve an improvement of 3 points in POEM was established (81)
Mean change from baseline in CDLQI and IDQOL	For both CDLQI and IDQOL, values after first rescue treatment used were set to missing. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, AEs and lack of efficacy were imputed by WOCF or baseline value if there was no post-baseline value. Patients with missing values due to other reasons, including COVID-19, were imputed by MI. All non-missing data before imputation of WOCF were used for MI. In MI,	The CDLQI is a validated questionnaire designed to measure the impact of skin disease on QoL in children ≥4 years of age (72). The IDQOL is a validated questionnaire developed to measure the impact of skin disease on the QoL of infants and preschool children <4 years of age (74)	The CDLQI is designed to measure the impact of skin disease on QoL in children ≥4 years of age (72). The IDQOL is a questionnaire developed to measure the impact of skin disease on the QoL of infants and preschool children <4 years of age (74). No MCID for CDLQI has been established for dermatologic conditions but for children with AD, 6-8 points have been suggested (84,85). In the evaluation of dupilumab for children aged 6-11, a MCID of 6 points was stated

Outcome measure	Definition	Validity	Clinical relevance
	the seed numbers were 12345 and 54321 with imputation size 40		
Proportion of patients who achieve a change of at least 3 points on the NRS	Defined as a reduction of ≥3 points from baseline in the weekly average of daily worst scratch/itch NRS score	The NRS was validated in Phan et al. 2012 (86)	The NRS measures itch using a worst scratch/itch NRS that was developed and tested for the study-relevant age group. This is an 11-point scale (0 to 10) in which 0 indicates no scratching/itching, while 10 indicates worst scratching/itching possible. Patients are asked to rate the intensity of their itch in the last 24 hours using this scale. It features high reliability and concurrent validity and is a popular choice for all patients due to its simple format (86). No MCID for NRS has been established for children. In a previous DMC evaluation of dupilumab (12-17 year olds), a MCID of 10 percentage points in the proportion achieving a reduction of at least 3 points was established (82)

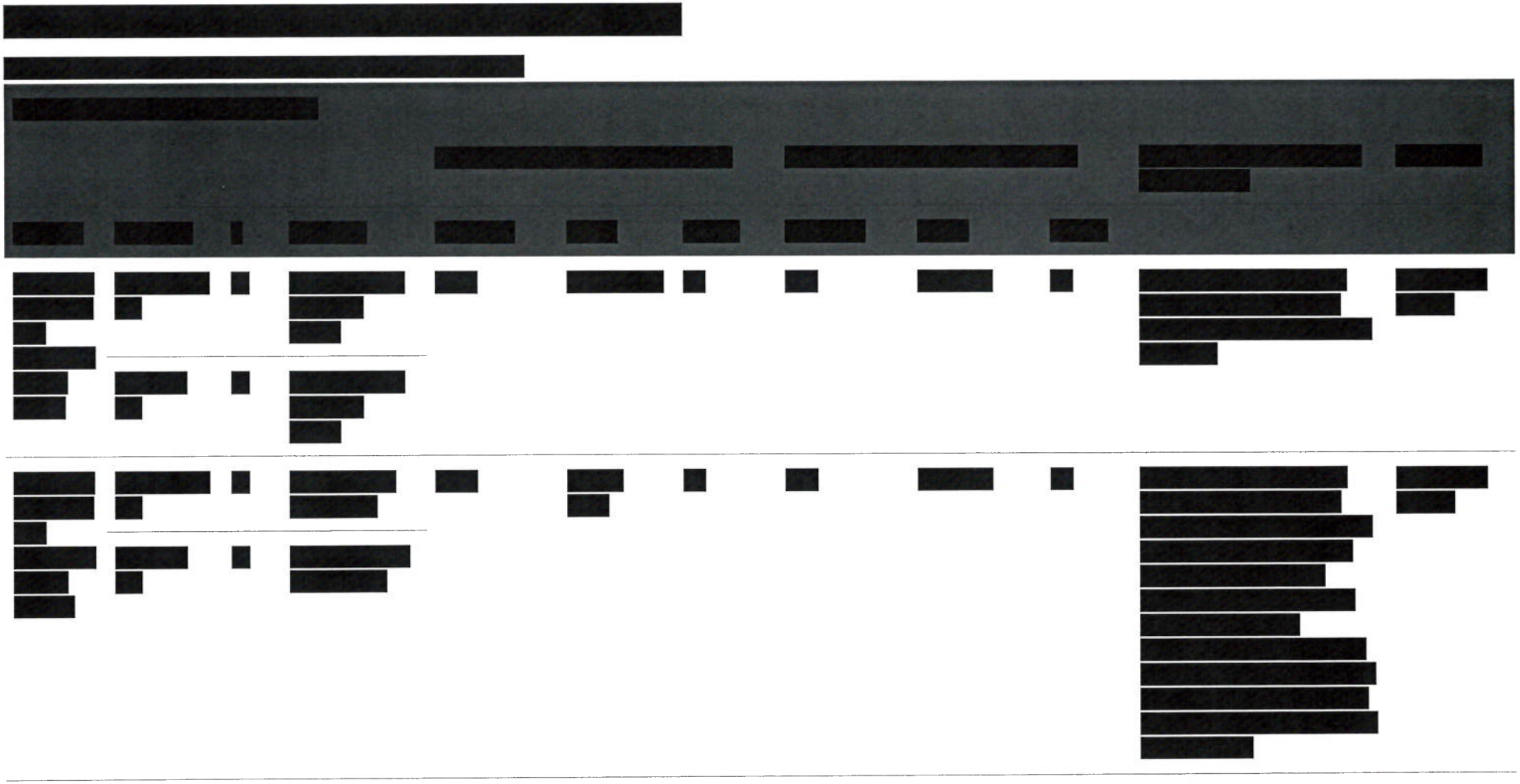
Results per study

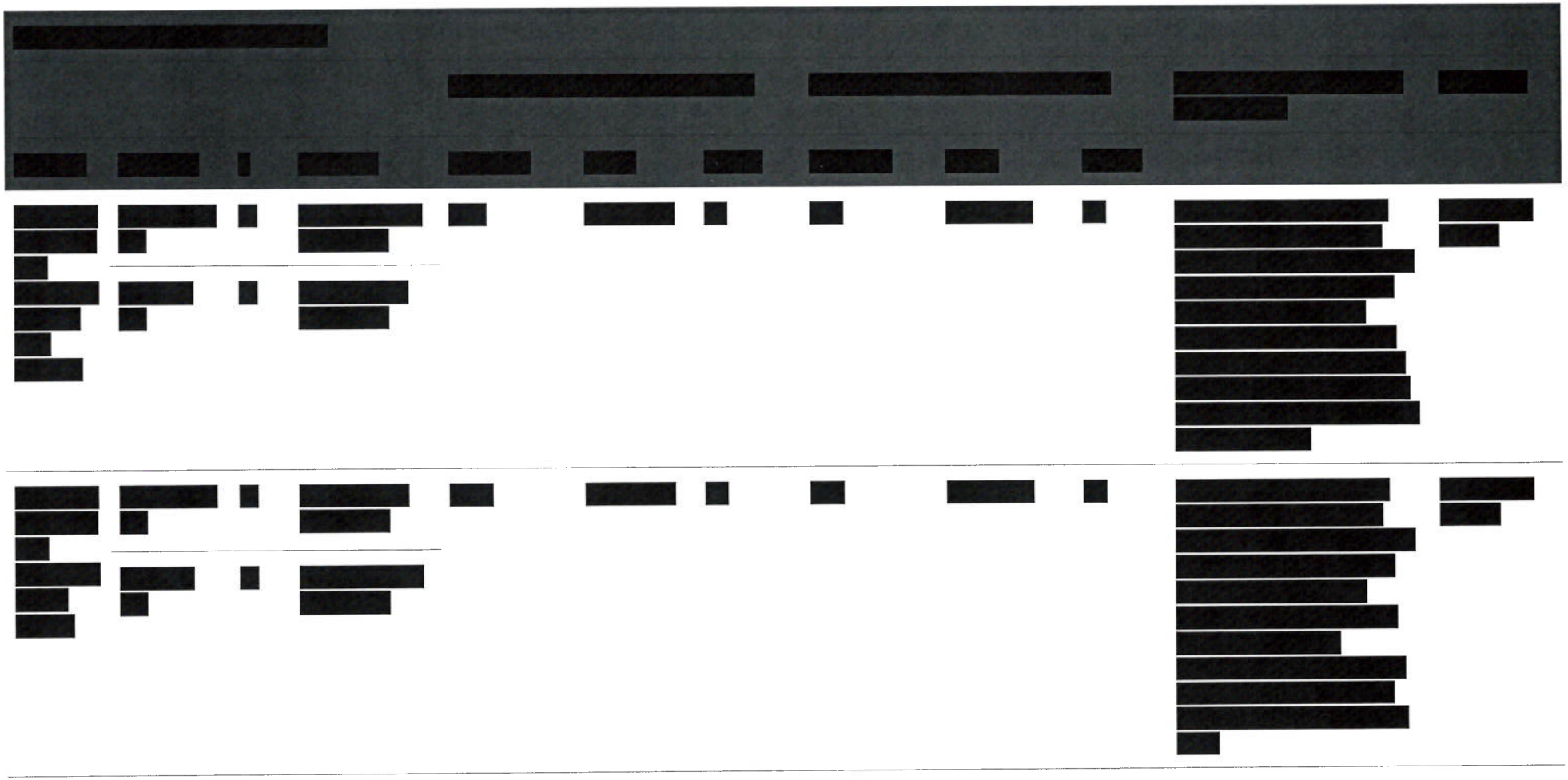
Table 57: Results per study from LIBERTY AD PRESCHOOL trial

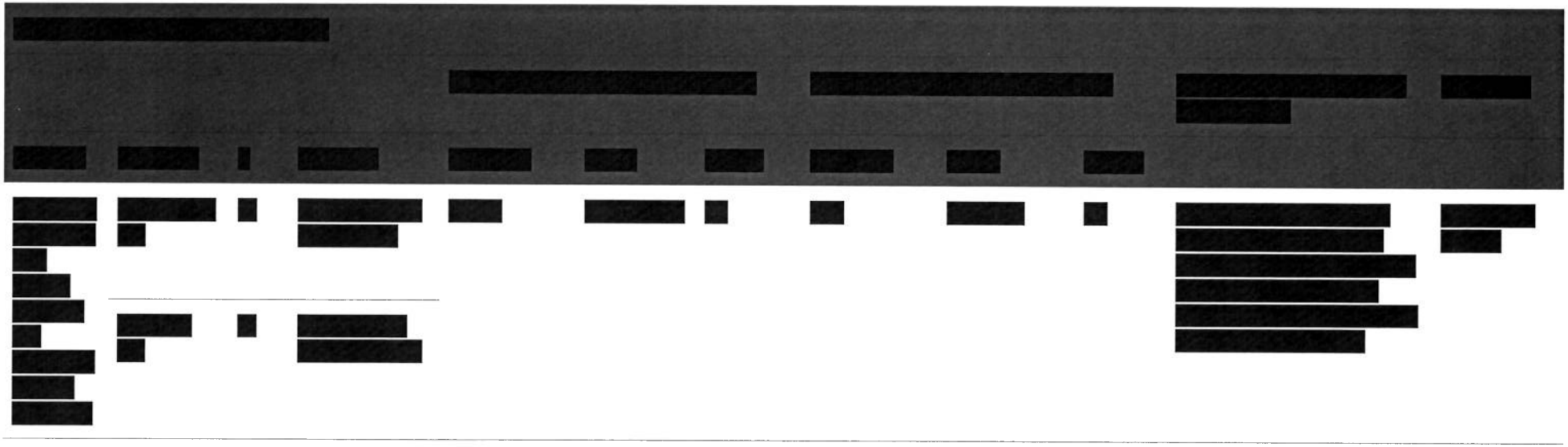
LIBERTY AD PRESCHOOL (NCT03346434)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P*-value	Difference	95% CI	*P*-value		
Proportion of patients who achieve at least 75% eczema reduction on the EASI scale	Dupilumab + TCS	63	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	Difference in proportions is presented and the relative difference as a risk ratio is also presented	CSR data on file (68)
	Placebo + TCS	62	[redacted]								
Mean reduction in EASI from baseline to week 16	Dupilumab + TCS	63	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA	Mean % change (SD) is presented, and the LS mean difference	CSR data on file (68)
	Placebo + TCS	62	[redacted]								
Proportion of patients	Dupilumab + TCS	63	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA	Difference in proportions is presented and the relative	CSR data on file (68)

LIBERTY AD PRESCHOOL (NCT03346434)												
				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		
who achieve at least a 50% eczema reduction on the SCORAD scale	[redacted]	[redacted]	[redacted]							difference as a risk ratio is also presented	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LIBERTY AD PRESCHOOL (NCT03346434)											
				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		
[redacted]											
[redacted]											







Appendix F Comparative analysis of efficacy and safety

This section has not been filled out, as the comparative analysis presented in the current application is a direct comparative analysis. Thus, all comparative results were presented in Appendix E.

Appendix G Extrapolation

NA

Appendix H – Literature search for HRQoL data

NA

Appendix I Mapping of HRQoL data

NA

Appendix J Probabilistic sensitivity analyses

NA