26 February 2026
EMADOC-1700519818-2983059
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dupixent

International non-proprietary name: Dupilumab

Procedure No. EMA/VR/0000282164

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AD	atopic dermatitis
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
C-DLQI	Children's Dermatology Life Quality Index
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
Cmax	maximum concentration
CSR	clinical study report
CSU	chronic spontaneous urticaria
EAACI	European Academy of Allergology and Clinical Immunology
EDF	European Dermatology Forum
EoE	eosinophilic esophagitis
E-R	exposure-response
FcεRI	Fc epsilon receptor
GA2LEN	Global Allergy and Asthma European Network
GCP	Good Clinical Practice
HRQoL	health-related quality of life
HSS7	hive severity score over 7 days
ICH	International Council for Harmonization
IDQOL	Infant's Dermatitis Life Quality Index
Ig	immunoglobulin
IL	interleukin
IMP	investigational medicinal product
ISS7	itch severity score over 7 days
ITT	intent-to-treat
LD	loading dose
mUAS7	modified urticaria activity score over 7 days
NAb	neutralizing antibody
PCSA	potentially clinically significant abnormality
PD	pharmacodynamic
PK	pharmacokinetics
PN	prurigo nodularis
PRO	patient reported outcome
q2w	every 2 weeks
q4w	every 4 weeks
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
Th	T-helper
UAS7	Urticaria Activity Score over 7 days
ULN	upper limit of normal

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Sanofi Winthrop Industrie submitted to the European Medicines Agency on 30 June 2025 an application for a variation.

The following variation was requested:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include treatment of moderate to severe chronic spontaneous urticaria (CSU) in children aged 2 to 11 years whose disease is inadequately controlled by H1 antihistamines and who are naive to anti-IgE therapy for CSU for DUPIXENT, based on the results from study PKM16982; this is a multi-center, single-arm study to investigate the pharmacokinetics and safety of dupilumab in male and female participants ≥2 years to <12 years of age with uncontrolled chronic spontaneous urticaria (CSU). Consequently, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 14.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0353/2024 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0353/2024 has been completed.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	30 June 2025
Start of procedure:	19 July 2025
CHMP Rapporteur Assessment Report	12 September 2025

Timetable	Actual dates
PRAC Rapporteur Assessment Report	17 September 2025
PRAC Outcome	2 October 2025
CHMP members comments	6 October 2025
Updated CHMP Rapporteur(s) (Joint) Assessment Report	9 October 2025
Request for supplementary information (RSI)	16 October 2025
MAH's responses submitted to the CHMP on	26 November 2025
CHMP Rapporteur Assessment Report	6 January 2026
PRAC Rapporteur Assessment Report	7 January 2026
PRAC members comments	n/a
PRAC Outcome	15 January 2026
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	n/a
Request for supplementary information (RSI)	29 January 2026
MAH's responses submitted to the CHMP on	2 February 2026
CHMP-PRAC Rapporteur Assessment Report	11 February 2026
CHMP-PRAC members comments	n/a
Updated CHMP-PRAC Rapporteur Assessment Report	19 February 2026
CHMP Opinion	26 February 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Chronic spontaneous urticaria (CSU), also known as chronic idiopathic urticaria, is characterized by the spontaneous appearance of pruritic wheals (hives) and flare-type skin reactions without a specific known cause that persists for more than 6 weeks, and which may be accompanied by angioedema. Wheals and pruritus represent the key urticaria symptoms. Owing to the unpredictability of the occurrence of pruritic wheals, the disease can have a substantial impact on patients' daily life. Significant exacerbations of chronic urticaria may result in emergency room visits and hospitalizations.

State the claimed the therapeutic indication

The new indication statement initially proposed for this submission is as follows:

Dupixent is indicated for the treatment of moderate to severe chronic spontaneous urticaria in adults, adolescents and children 2 years and older, whose disease is inadequately controlled by H1 antihistamines and who are naive to anti-IgE therapy for CSU.

The indication was discussed during the procedure and was aligned with the Dupixent adult and adolescents CSU indication. The final approved indication is as follows:

Dupixent is indicated for the treatment of moderate to severe chronic spontaneous urticaria in adults, adolescents, and children (2 years and above) with inadequate response to H1 antihistamines and who are naive to anti-IgE therapy for CSU.

Epidemiology and risk factors

CSU is a globally prevalent, debilitating skin condition that affects both adults and children. The disease can develop at any age, but is rarely diagnosed before the age of 2 years. The duration of the disease is generally several years but is likely to be longer in more severe cases, in cases with concurrent angioedema and in cases of comorbid inducible urticaria.

The prevalence and incidence of CSU are not precisely known and show considerable regional differences while studies reporting the incidence and prevalence of CSU in children are scarce. A recent systematic review with meta-analysis indicates a point prevalence of chronic urticaria (including both entities, chronic spontaneous urticaria and chronic inducible urticaria) in Europe of 0.5% (95% CI: 0.2-1.0), in North America of 0.1% (95% CI: 0.1-0.1), and with the highest point prevalence of 1.4% (95% CI: 0.5-2.9) in Asian countries (Fricke et al., 2019). European and Asian studies have estimated a point prevalence of 0.1% to 0.6% for children.[1]

Aetiology and pathogenesis

CSU results from pathogenic activation of mast cells (MCs) and basophils. Still, disease pathophysiology is not fully elucidated. Activation of the high-affinity IgE receptor, FcεR1, is an important step in the development of CSU. The degranulation of skin mast cells leading to release of histamine is considered to be the initial event in the development of skin change. Higher levels of histamine release from mast cells have been observed in skin biopsies from patients with CSU. Unlike normal skin, patients with active CSU show deposition of basophils in skin and associated basopenia in blood.

Based on current knowledge, CSU pathogenesis is believed to be similar in adults and adolescents and children, while adolescent CSU exhibit clinical characteristics closer to adults CSU as compared to paediatric CSU. Pathologic activation of mast cells and basophils in patients with CSU is thought to occur via autoimmune and non-autoimmune mechanisms. In the non-autoimmune process, inappropriate activation of mast molecules (such as SYK) promotes spontaneous degranulation of mast cells/basophils with subsequent release of histamine and other mediators. Based on recent evidence, two autoimmune endotypes have been described as type I "autoallergic" (which is associated with IgE antibodies against autoantigens) and type IIb autoimmune (which is driven by autoantibodies to FceR1 and/or IgE). Regional differences for autoimmune CSU endotypes are not well researched and understood.

[1] Fricke J, Ávila G, Keller T, Weller K, Lau S, Maurer M, et al. Prevalence of chronic urticaria in children and adults across the globe: Systematic review with meta-analysis. Allergy. 2020;75(2):423-32

Clinical presentation, diagnosis

CSU is characterized by the spontaneous appearance of pruritic wheals (hives) and flare-type skin reactions without a specific known cause that persists for more than 6 weeks, which can also be accompanied by angioedema. The clinical presentation is similar across age ranges with some notable differences in children compared to adults and adolescents (ie. less female predominance, higher incidence of atopic comorbidities [allergic rhinitis, asthma, etc.], lower incidence of angioedema and antithyroid antibodies, and better response to antihistamine therapy).

Studies in the paediatric age group show that 17% to 33% of children with CSU go into remission within the first year and 39% to 54% do so within the first 3 years. Paediatric patients with CSU are known to spontaneously go into remission over time, however, recurrence can happen after remission.

The diagnostic approaches for CSU in adults, adolescents, and children are similar. The diagnosis of CSU is based on a detailed medical history (duration of episodic and transient wheals for a period of 6 weeks or longer, use of medications, physical stimuli) and careful physical examination (characteristic erythematous, edematous wheals that wax and wane rapidly, with or without accompanying angioedema). Urticaria in CSU needs to be differentiated from other medical conditions where wheals, angioedema, or both can occur, for example anaphylaxis, autoimmune disorders, or bradykinin-mediated angioedema including hereditary angioedema.

Management

The treatment approaches for CSU in children (<12 years of age) are similar to adults and adolescents but have been largely extrapolated from adults as studies in children are scares. Importantly, biologics are not approved for treatment of CSU in children aged <12 years. The updated international guidelines (Zuberbier et al., 2022[2]) recommend a stepwise treatment. Step 1 treatment starts with non-sedating H1-antihistamines at approved doses. If symptoms are inadequately controlled after 2 to 4 weeks, an increase in H1-antihistamine dose up to 4-fold (unapproved dose) is recommended (Step 2). If symptoms remain uncontrolled or intolerable, omalizumab (anti-IgE) should be added in patients >12 years of age (Step 3). Of note, Step 3 does not apply for children <12 years of age. Beyond this, Step 4 treatment options include add-on ciclosporin A, or montelukast (leukotriene receptor antagonist) to H1 antihistamines.

Unmet medical need

CSU has a profound impact on children's quality-of-life including anxiety and psychological symptoms, notably impacting sleep and school attendance. Studies evaluating the response to antihistamines are limited but available reports suggest that approximately 10% of children on high-dose H1-antihistamines still remain symptomatic (Gabrielli et al., Özçeker et al)[3]. Although anti-IgE therapy with omalizumab is approved for CSU patients ≥12 years, there are no approved biologic therapies for children below this age. For the antihistamine refractory paediatric population, off-label cyclosporine is recommended in clinical guidelines but has a high incidence of dose dependent adverse effects

[2] Zuberbier T, Abdul Latiff AH, Abuzakouk M, Aquilina S, Asero R, Baker D, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2022;77(3):734-66.
Joint initiative of the Dermatology Section of the European Academy of Allergology and Clinical Immunology (EAACI), the Global Allergy and Asthma European Network (GA²LEN) and its Urticaria and Angioedema Centers of Reference and Excellence (UCAREs and ACAREs), the European Dermatology Forum (EDF; EuroGuiDerm), and the Asia Pacific Association of Allergy, Asthma and Clinical Immunology

[3] Gabrielli, S., Le, M., Netchiporouk, E., Miedzybrodzki, B., Baum, S., Greenberger, S., Staubach-Renz, P., & Ben-Shoshan, M. (2020). Chronic urticaria in children can be controlled effectively with updosing second-generation antihistamines. Journal of the American Academy of Dermatology, 82(6), 1535–1537.
Özçeker, D., Can, P. K., Terzi, Ö., Ornek, S. A., Değirmentepe, E. N., Kızıltac, K., Sarac, E., & Kocatürk, E. (2023). Differences between adult and paediatric chronic spontaneous urticaria from a cohort of 751 patients: Clinical features, associated conditions and indicators of treatment response. Paediatric allergy and immunology :34(2), e13925.

including renal dysfunction, hypertension, and increased risk of malignancy. Other alternative agents such as antidepressant and immunosuppressants have little data on efficacy. Based on the reasoning above, there is a substantial therapeutic need for new therapeutic options in children below 12 years of age with CSU who are refractory to antihistamine treatment.

2.1.2. About the product

Dupixent (dupilumab) is a human monoclonal IgG4 antibody that inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the Type I receptor and both IL-4 and IL-13 signaling through the Type II receptor. By blocking signaling of both IL-4 and IL-13 which are key cytokines involved in type 2 inflammation, dupilumab broadly suppresses type 2 inflammation.

Dupilumab is approved in the EU for the following indications:

- Atopic dermatitis

Adults and adolescents

Dupixent is indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy.

Children 6 months to 11 years of age

Dupixent is indicated for the treatment of severe atopic dermatitis in children 6 months to 11 years old who are candidates for systemic therapy.

- - Asthma

Adults and adolescents

Dupixent is indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide who are inadequately controlled with high dose inhaled corticosteroids plus another medicinal product for maintenance treatment.

Children 6 to 11 years of age

Dupixent is indicated in children 6 to 11 years old as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide who are inadequately controlled with medium to high dose inhaled corticosteroids plus another medicinal product for maintenance treatment.

- - Chronic rhinosinusitis with nasal polyposis (CRSwNP)

Dupixent 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

Dupixent is indicated for the treatment of adults with moderate-to-severe prurigo nodularis who are candidates for systemic therapy.

- - Eosinophilic esophagitis (EoE)

Dupixent is indicated for the treatment of eosinophilic esophagitis in adults, adolescents and children aged 1 year and older, weighing at least 15 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy.

- - Chronic obstructive pulmonary disease (COPD)

Dupixent is indicated in adults as add-on maintenance treatment for uncontrolled chronic obstructive pulmonary disease (COPD) characterised by raised blood eosinophils on a combination of an inhaled corticosteroid (ICS), a long-acting beta2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA), or on a combination of a LABA and a LAMA if ICS is not appropriate.

- - Chronic Spontaneous Urticaria

Dupixent is indicated for the treatment of moderate to severe chronic spontaneous urticaria in adult and adolescent (**12 years and above**) patients with inadequate response to H1 antihistamines and who are naive to anti-IgE therapy for CSU

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The paediatric investigation plan EMEA-001501-PIP07-20-M02 in its latest modification from 2024 have been reviewed and accepted by the Paediatric Committee of EMA (PDCO). The PIP includes the clinical studies EFC16461 (Study A, B, and C) as well as the PK study PKM16982 overall enrolling children with CSU with an age range between 2 and 17 years.

Dupilumab PK and response data in paediatric patients aged 2 to <12 years are part of the extrapolation plan of efficacy from adults /adolescents to the paediatric population. The PD endpoints in exposure-response analyses were planned to support the assumption that the exposure-response relationships at the selected doses are similar in children from 2 years to less than 12 years of age and in adult / adolescent patients with CSU.

During the conduct of study PKM16982, the sponsor encountered challenges in the enrolment of patients in the younger age group (2 to less than 6 years). A reduction of in the patient number was therefore proposed to PDCO, which was accepted, but it was noted that especially for the younger age subset (2 to <6 years) clinical data to support the extrapolation will be very limited.

2.2. Non-clinical aspects/ Quality aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

The applicant provided in section 3.2.R the Justification for no need of Notified Body Opinion - MDR Article 117. The applicant sufficiently outlined that there are no changes to the design or intended purpose of the device (200mg and 300mg PFS-S and PFP presentations), nor is there a new medical device being introduced. The justification for not providing the notified body opinion is acceptable.

The applicant sufficiently outlined that the characteristics of the intended user and use environment for the CSU paediatric patient population is supported by existing usability data for the authorized presentations. Indeed, dupilumab is a water soluble monoclonal antibody which undergoes extensive *in vivo* metabolism. The human excretion products of dupilumab are predicted to be rapidly and readily degraded in sewage collection and treatment systems and in the environment. Therefore, dupilumab is unlikely to result in a significant risk to the environment.

It can be agreed that an additional usability study is not required.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1. Overview of paediatric Phase 3 CSU studies of the dossier

Study number/ status at submission	Study objective	Treatment/ follow-up duration	Participants randomized/ treated
PKM16982 (CUPIDKids) Completed [PKM16982] and [PKM16982-Addendum]	To characterize the serum concentration of dupilumab over time in paediatric participants with CSU who remain symptomatic despite the use of H1-antihistamines.	24/12 weeks	Enrolled/treated: 15/15 (**dupilumab: 15**)
EFC16461 (CUPID) Study A Completed Previously submitted CSR EFC16461 Study A	Efficacy and safety of dupilumab compared to placebo in participants with CSU who remain symptomatic despite the use of H1-antihistamines.	24/12 weeks	Randomized/treated: 138/138 (dupilumab: 70[a], Placebo: 68[a]) **Children (≥6 to <12 years): 2 (dupilumab: 2[a] Placebo: 0)**
EFC16461 (CUPID) Study C Completed Previously submitted CSR EFC16461 Study C and EFC16461 Study C-Addendum	Same as EFC16461 Study A	24/12 weeks	Randomized/treated: 151/151 (dupilumab: 74[a], Placebo: 77[a]) **Children (≥6 to <12 years): 3 (dupilumab: 1[a] Placebo: 2[a])**

Abbreviations: CSU: Chronic spontaneous urticaria.
a As treated.

The paediatric clinical development program for dupilumab in CSU in children aged ≥2 to <12 years was designed based on an extrapolation approach and consists of 3 studies, each with 24-week treatment periods: A Phase 3 PK/safety **Study PKM16982** in paediatrics that included 15 participants (≥2 to <12 years of age) and 2 independent Phase 3 studies conducted under the master protocol EFC16461 (**Study A and Study C**) that included 5 children aged ≥6 to <12 years along with adults and adolescents.

According to the applicant, the extrapolation approach is supported by the following assumptions:

1. Similarity of CSU disease pathogenesis, progression and clinical manifestation in paediatric patients ≥2 to <12 years old when compared to adults and adolescents.

2. Similar treatment guidelines and response to interventions for CSU in paediatric and adult patients.
3. Well characterized PK profile of dupilumab with similar trend E-R relationships in paediatric and adult patients with AD, asthma, and EoE.

Data generated in a clinical study in adults and adolescents with CSU (EFC16461 Study A and Study C) together with the overall dupilumab clinical and safety data in paediatric patients with AD, asthma, and EoE were considered in order to support extrapolation of efficacy from adults to children age ≥2 to <12 years of age with CSU.

2.3.2. Pharmacokinetics in children aged ≥2 to < 12 years with CSU

The PK of dupilumab in serum has previously been described in adults and adolescents with CSU (procedure EMA/VR/0000257461) as well as in healthy subjects and in patients with AD, asthma, CRSwNP, EoE, PN, and COPD. In general, the PK of dupilumab is best described with parallel linear and non-linear, target-mediated elimination. Following SC administration, the concentration-time profile of dupilumab is characterized by an absorption phase (median Tmax of 3 to 7 days) followed by a multi-exponential elimination phase. At higher target-saturating concentrations, the initial slower elimination phase is linear, presumably mediated mostly by nonspecific catabolic processes, followed by a rapid terminal nonlinear, saturable target-mediated elimination phase at lower concentrations. The most notable factor explaining variability in dupilumab disposition is body weight.

The proposed dupilumab SC dose regimens in children with CSU are as follows

- 200 mg q4w with no loading dose in children with body weight ≥5 kg to <15 kg.
- 300 mg q4w with no loading dose in children with body weight ≥15 kg to <30 kg, aged ≥2 to <6 years old.
- 300 mg q4w with an initial 300 mg on Day 1 followed by a second 300 mg on Day 15, then 300 mg q4w starting 4 weeks after Day 15, in children with body weight ≥15 kg and <30 kg, aged ≥6 to <12 years old.
- 200 mg q2w with an initial 400 mg loading dose in children with body weight ≥30 kg to <60 kg.
- 300 mg q2w with an initial 600 mg loading dose in children with body weight ≥60 kg, aged ≥6 to <12 years old.

The number of children ≥2 to <12 years with CSU by age/weight and dose regimen in the clinical trial programme are summarised in the Table 2 below.

Table 2. Dosing regimen in children ≥2 to <12 years of age with CSU in clinical study programme

Treatment	Body weight	Age	Initial dose	Subsequent dose	Number of study participants			
					PKM16982	Study A	Study C	Total
Dupilumab	5 kg to <15 kg	≥2 to <12 years	200 mg (one 200 mg injection)	200 mg q4w	1	0	0	1

Treatment	Body weight	Age	Initial dose	Subsequent dose	Number of study participants			
					PKM16982	Study A	Study C	Total
	15 kg to <30 kg	≥2 to <6 years	300 mg (one 300 mg injection)	300 mg q4w	4	0	0	4
		≥6 to <12 years	600 mg (two 300 mg injections)	300 mg q4w	2	0	0	2
	30 kg to <60 kg	≥2 to <12 years	400 mg (two 200 mg injections)	200 mg q2w	8	2	1	11
Dupilumab (Pool)	5 kg to <60 kg	≥2 to <12 years			15	2	1	18
Placebo	30 kg to <60 kg	≥2 to <12 years	Placebo	Placebo	0	0	2	2
q2w: once every 2 weeks; q4w: once every 4 weeks;								

1. Bioanalytical methods

All methods used to assess functional dupilumab concentration and the immunogenicity to dupilumab (ADA and NAb) in samples collected from PKM16982 and EFC16461 Study A and Study C are the same as previously described in detail in the original marketing application for adult AD and in the subsequent adult and adolescent asthma marketing application. The methods were validated according to regulatory guidance, and the performance characteristics of each bioanalytical method were validated with respect to a set of predefined validation parameters to demonstrate suitability for the quantification of analytes in human samples.

Serum samples for quantitation of functional dupilumab (i.e., dupilumab with 1 or both binding sites available for target IL4Rα binding) in human serum were analysed using validated ELISAs with a LLOQ of functional dupilumab of 0.078 mg/L in undiluted human serum.

ADAs were assessed in serum samples using validated, non-quantitative, titer-based, electrochemiluminescence bridging immunoassays. Neutralizing antibody activity would have been assessed in samples that would have been confirmed positive in the ADA assay using a validated competitive ligand binding assay.

Bioanalytical reports for EFC16461 Study A and Study C were assessed in procedure EMA/VR/0000257461 and did not raise concern. Bioanalytical report for PKM16982 was provided during this current procedure. All analytical runs for functional dupilumab concentration assay and anti-dupilumab assay fulfilled criteria from ICH guideline M10 on bioanalytical method validation and study sample analysis and thus, were found acceptable. Incurred sample reanalysis confirmed reproducibility of the functional dupilumab concentration assay.

2. Pharmacokinetic data analysis

Descriptive statistics were used to summarize the concentration data over time in patients with CSU. Dupilumab concentrations determined in children ≥2 to <12 years of age with CSU were also compared to data from adults and adolescents with CSU in Phase 3 studies as well as children <12 years of age with the AD, asthma, and EoE at the relevant dose regimens.

A **population PK analysis** was conducted with data in children ≥2 to <12 years of age with CSU using the maximum a posteriori (MAP) Bayesian approach, which allowed for the incorporation of prior information from an established global paediatric popPK model based on all available paediatric PK data from previously approved paediatric indications [atopic dermatitis (AD), asthma, and eosinophilic esophagitis (EoE)] for dupilumab in children aged from 6 months to <12 years.

The final pooled paediatric dataset included 3748 PK concentrations from 1019 paediatric patients aged < 12 years old, 544 children with AD (aged ≥6 months to <12 years), 377 children with asthma (aged ≥6 to <12 years), and 98 children with EoE (aged ≥1 to <12 years).

Table 3. Description of studies included in global paediatric Pop PK model

Study Number	Phase	Treatment group	Duration	Population (N)	PK Samples[b]
R668-AD-1412	2a	Part A: SC: 2 mg/kg or 4 mg/kg single dose (capped at 300 mg) Part B: 2 mg/kg or 4 mg/kg QW (capped at 300 mg)	Part A: Single dose; Part B: 4 weeks	Paediatric AD patients aged ≥6 to <12years[a] (N=37)	Part A: Semi-dense Part B: Sparse
R668-AD-1539	2/3	Part A: SC: 3 mg/kg or 6 mg/kg single dose Part B: SC q4w: ≥5 kg to <15 kg: 200 mg SC q4w: ≥15 kg to <30 kg: 300 mg	Part A: Single dose; Part B: 16 weeks	Paediatric AD patients aged ≥6 months to <6 years (N=188)	Part A: Semi-dense Part B: Sparse
R668-AD-1652	3	SC: ≥15 kg to <30 kg: 100 mg q2w (with a loading dose of 200 mg) SC: ≥30 kg: 200 mg q2w (with a loading dose of 400 mg) SC: ≥15 kg: 300 mg q4w (with a loading dose of 600 mg)	16 weeks	Paediatric AD patients aged ≥6 to <12 years (N=319)	Sparse
EFC14153	3	200 mg q2w SC (>30 kg) 100 mg q2w SC (≤30 kg)	52 weeks	Paediatric asthma patients aged ≥6 to <12 years (N=268)	Sparse
LTS14424	3	200 mg q2w SC (>30 kg) 100 mg q2w SC (≤30 kg) or 300 mg q4w SC (≤30 kg)	52 weeks	Paediatric asthma patients aged ≥6 to <12 years who rolled over from study EFC14153 (N=109 additional)[c]	Sparse

Study Number	Phase	Treatment group	Duration	Population (N)	PK Samples[b]
R668-EE-1877	3	Higher exposure dupilumab for Parts A and B: 5 to <15 kg-100 mg q2w SC 15 to <30 kg-200 mg q2w SC 30 to <60 kg-300 mg q2w SC ≥60 kg-300 mg qw SC (Part B) Lower exposure dupilumab for Parts A and B: 5 to <15 kg-200 mg q4w SC 15 to <30 kg-300 mg q4w SC 30 to <60 kg-200 mg q2w SC ≥60 kg-300 mg q2w SC (Part B)	16 weeks for Part A extended to 52 weeks in Part B	Paediatric EoE Patients aged ≥1 to <12 years (N=98)	Sparse

Abbreviation: AD: Atopic dermatitis; EoE: eosinophilic esophagitis; N: subject number in final pooled dataset; qw: every week; q2w: every two weeks; q4w: every four weeks.
a In study R668-AD-1412, the study population included paediatric AD patients aged ≥ 6 to <18 years. However, only paediatric AD patients aged <12 years were included in this global paediatric Pop PK model.
b See PK sampling time points in each study protocol.
c In study LTS14424, there were additional 109 placebo patients who rolled over from study EFC14153. There were also the other 210 patients in study LTS14424 who were rolled over from dupilumab treatment group of EFC14153 study.

Table 4. Descriptive statistics of potential continuous covariates for children <12 years of age in the final pooled dataset (N=1019)

Covariate at baseline	AD	Asthma	EoE	Total
Weight (kg)				
N	544	377	98	1019
Mean (SD)	26.3 (11.1)	35.7 (10.3)	27.2 (11.2)	29.8 (11.7)
Median (Min, Max)	24.1 (7.4, 79.1)	35 (16.4, 67.2)	25.4 (9.8, 59.9)	28.5 (7.4, 79.1)
Age (year)				
N	544	377	98	1019
Mean (SD)	6.85 (2.8)	8.87 (1.63)	7.11 (3.09)	7.62 (2.64)
Median (Min, Max)	7 (0.5, 11.9)	9 (6, 11)	8 (1, 11.4)	8 (0.5, 11.9)
Albumin (g/L)				
N	544	377	98	1019
Mean (SD)	46 (3.49)	46.8 (2.92)	45.9 (2.4)	46.3 (3.22)
Median (Min, Max)	46 (32, 54)	47 (35, 54)	46 (40, 56)	46 (32, 56)

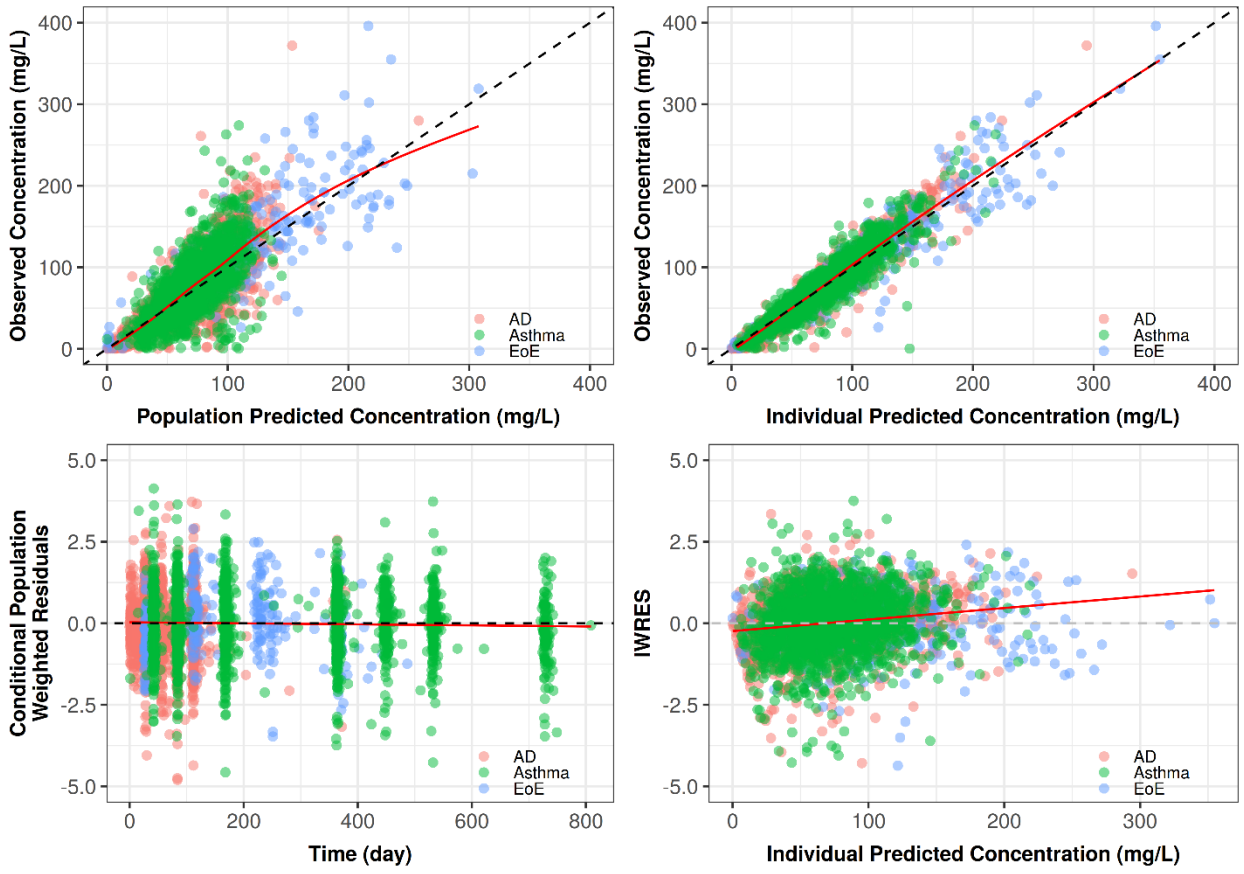
Abbreviations: AD: Atopic dermatitis; EoE: eosinophilic esophagitis; N: number of subjects; SD: standard deviation; Min: minimum; Max: maximum.

Base model

Considering the similarity of dupilumab PK across indications, the knowledge gained from a previously developed dupilumab global Pop PK base model (based on pooled data from 6 studies in healthy subjects, 10 studies in AD adult patients and 4 studies in asthma adult and adolescent patients; Study POH0668) was utilized for the current global paediatric Pop PK model development in children ≥6 months to <12 years of age. Considering the sparse nature of the majority of PK data in children aged ≥6 months to <12 years with AD, asthma or EoE, this prior global (adult and adolescent) Pop PK based model was fitted to the PK data from 6 studies in children aged ≥6 months to <12 years with AD, asthma and EoE to estimate the key PK parameters (such as volume of central compartment [V2], linear elimination rate constant [Ke], its inter-individual variability [IIV], and allometric scaling factors), with other PK parameters fixed to values estimated from the global Pop PK base model (study POH0668). The semi-dense PK data including absorption phase PK samples from Part A of studies R668-AD-1412 and R668-AD-1539 in the pooled dataset enable estimation of the absorption rate constant (Ka) in the global paediatric Pop PK model. In contrast, Ka was fixed to the adult estimate in the asthma paediatric model (POH1176). Analyses were conducted to evaluate the impact of different combinations of estimating IIV for V2, Ke, Ka, and Vmax, and estimating allometric scaling factors on V2, Ke, and Vmax. The model estimating V2, Ke, Ka, IIV for V2 and Ke, and weight-effect exponents on V2 and Ke, with other parameters fixed to the global base model, was selected as the final paediatric base model due to precise parameter

The popPK base model using time-varying weight reduced the objective function value significantly and was chosen to be the final global paediatric base model.

Figure 1. Goodness-of-fit plots for global paediatric Pop PK base model with time-varying weight in children aged ≥6 months to <12 years



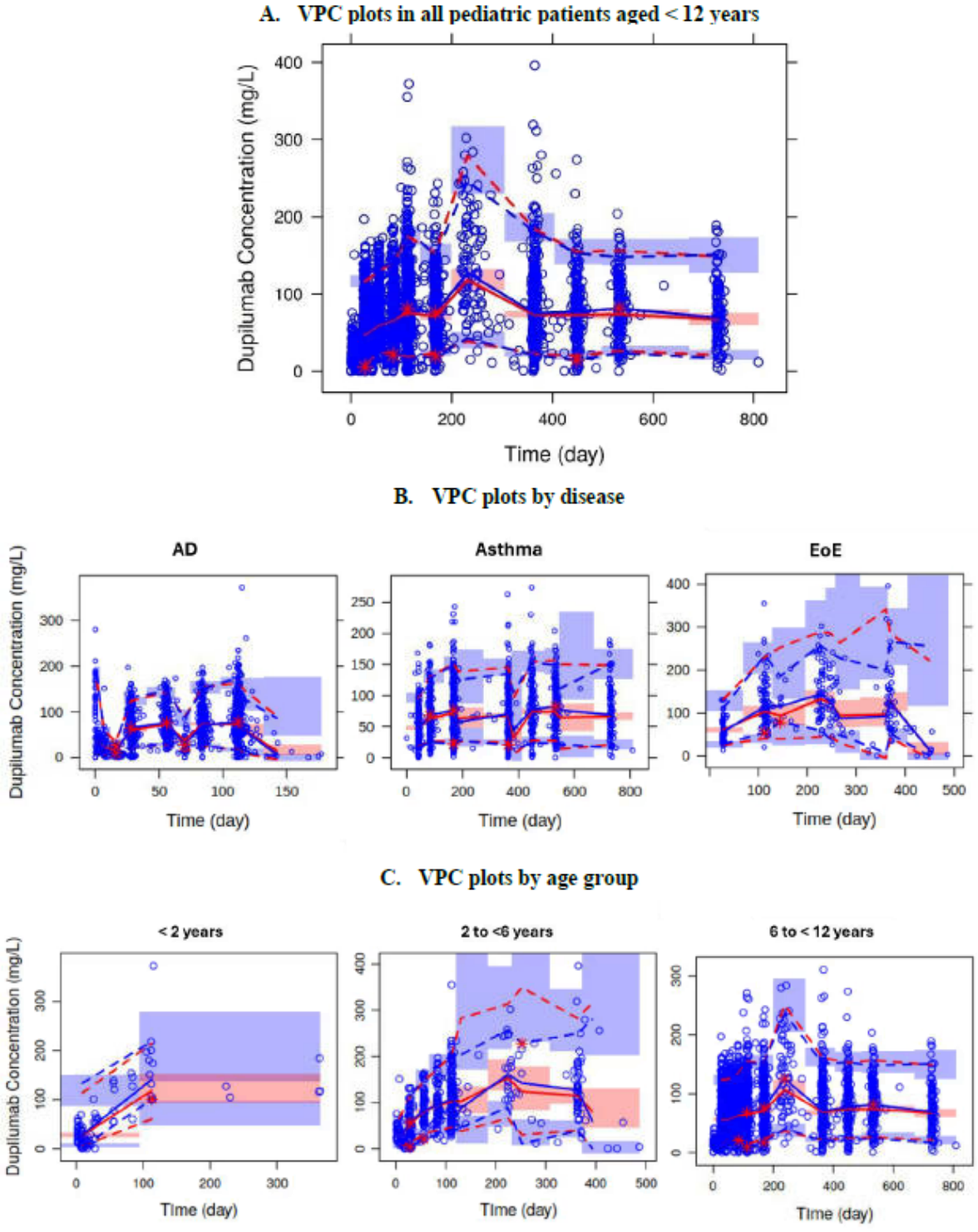
Covariate model development

After the identification of the final global paediatric base model, the development of the covariate model included an exploratory covariate analysis allowing identification of relationships between potential covariates and model parameters and the formal covariate analysis performed using a stepwise selection procedure. The SCM procedure involved stepwise testing of linear and non-linear relationships in a forward inclusion (ΔOFV of 6.63, $p < 0.01$ for 1 degree freedom [DF]) and backwards exclusion (ΔOFV of 10.8, $p < 0.001$ for 1 DF) procedure. The adaptive scope reduction (ASR) was used to improve the efficiency of the SCM by adaptively reducing the defined search scope during the forward search.

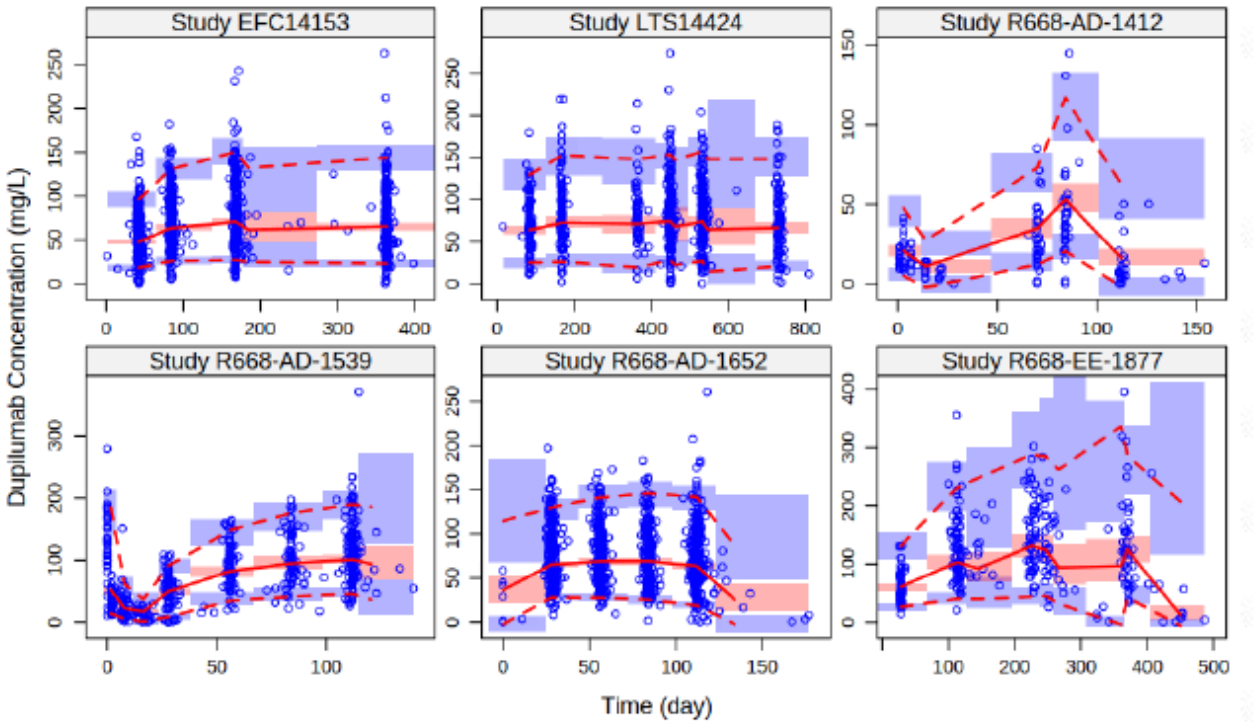
Besides body weight, the potential covariates were selected based on previous knowledge of covariate effects on dupilumab PK gained from paediatric models in AD, asthma, and EoE. The covariates evaluated in the exploratory and formal covariate analysis included baseline age, base albumin, race, gender, anti-drug antibody (ADA), and disease. Among the tested covariates, baseline albumin (on V2) and ADA (on Ke) were identified as statistically significant covariates on dupilumab PK in paediatric patients ≥6 months to <12 years of age. All other tested covariates, including baseline age, gender, race, and disease were not found to have statistically significant impact on dupilumab PK in the paediatric population.

The VPC plots for final global paediatric model in all paediatric patients and stratified by disease, age group or study were provided in the Figure 2 below, which indicated adequate stability and predictive performance of the final model.

Figure 2.Visual predictive checks for final global paediatric Pop PK model in paediatric patients aged <12 years



D. VPC plots by study



Legend: blue dots: observations; blue solid and dashed lines: the median and bounds (5th and 95th percentiles) of observed concentrations at each time bin; red solid and dashed lines: the median and bounds (5th and 95th percentiles) of predicted concentrations at each time bin; pink and light blue areas: confidence intervals of median and percentiles of predicted concentrations at each time bin.

Note: In study LTS14424, there were totally 309 pediatric patients with asthma.This included 210 patients who were rolled over from dupilumab treatment group of EFC14153 study (with PK data collection starting at >52 weeks in LTS14424) and an addtional 109 placebo patients who rolled over from study EFC14153 (with PK data collection starting at day 0 in LTS14424).

The PK parameter estimates and associated standard errors for the final global paediatric Pop PK model in paediatric patients aged <12 years with AD, asthma and EoE are provided below. All parameters were estimated with reasonable precision (%RSE < 50%).

The results of simulations to evaluate the impact of those statistically significant covariates on dupilumab PK revealed that only body weight exerted a notable effect explaining between-subject variability of dupilumab PK exposures in paediatric patients, while ADA and albumin have minimal clinically meaningful effect with less than 20% change in PK exposures relative to the typical paediatric patients.

Table 5. Parameter estimates and bootstrap results for final global pediatric Pop PK model in children aged <12 years

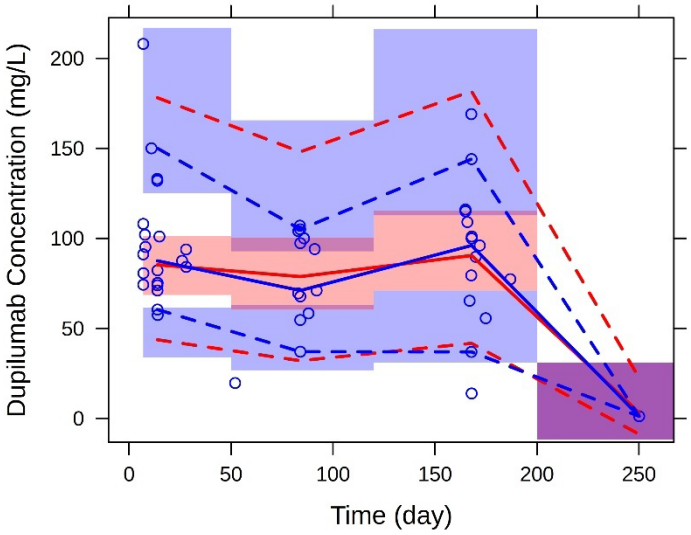
Parameter	Estimate	% RSE	[95%CI]	Bootstrap Median	Bootstrap [2.5th, 97.5 th]
Typical value of K_e (θ_1, 1/day)	0.0438	3.77%	[0.0405, 0.0471]	0.0437	[0.0392, 0.0487]
Typical value of V_2 (θ_2, L)	2.43	3.13%	[2.79, 2.58]	2.42	[2.21, 2.65]
Typical value of K_{23} (θ_3, 1/day)	0.089 (fix)	--	--	0.089 (fix)	--
Typical value of K_{32} (θ_4, 1/day)	0.15 (fix)	--	--	0.15 (fix)	--
Typical value of V_{max} (θ_5, mg/L/day)	1.48 (fix)	--	--	1.48 (fix)	--
Typical value of K_m (θ_6, mg/L)	2.52 (fix)	--	--	2.52 (fix)	--
Typical value of K_a (θ_7, 1/day)	0.667	7.49%	[0.567, 0.767]	0.670	[0.568, 0.808]
Typical value of F_{sc} (θ_8, %)	63 (fix)	--	--	63 (fix)	--
Power coefficient of weight on K_e	0.116	28.2%	[0.0504, 0.181]	0.113	[0.00512, 0.240]
Power coefficient of weight on V_2	0.739	6.01%	[0.686, 0.762]	0.738	[0.653, 0.829]
Power coefficient of weight on V_{max}	0.33 (fix)	--	--	0.33 (fix)	--
Power coefficient of ADA on K_e	0.286	12.5%	[0.215, 0.358]	0.286	[0.135, 0.465]
Power coefficient of ALB on V_2	-0.672	15.0%	[-0.873, -0.471]	-0.675	[-0.944, -0.459]
Inter-individual variability (CV%)					
IIV on K_e	19.8	9.29%	[17.9, 21.6] (32.0%)	19.5	[13.4, 24.3]
IIV on V_2	16.0	10.8%	[14.2, 17.7] (33.4%)	16.1	[12.3, 20.0]
Residual variability (RV)					
Proportional term	0.172	2.92%	[0.167, 0.177]	0.172	[0.156, 0.185]
Additive term (mg/L)	5.87	6.61%	[5.47, 6.25]	5.79	[4.89, 7.20]

Abbreviation: CI: confidence interval; CV: coefficient of variation; F_{sc}: bioavailability following SC administration; K_{23}, K_{32}: inter-compartment distribution rate constants; K_a: absorption rate constant ; K_e: linear elimination rate constant; K_m: Michaelis constant; V_2:volume of central compartment; V_3: volume of peripheral compartment; V_{max}: maximum target-mediated rate of elimination; RSE: percentage of relative standard error (100% * SE / estimate); SC: subcutaneous; θ: estimate of a Pop PK parameter.

The suitability of the global paediatric Pop PK model to describe dupilumab PK in 18 children ≥2 to <12 years of age with CSU from three clinical studies EFC16461 Study A (N=2), Study C (N=1), and PKM16982 (N=15) was assessed by visual predictive checks (VPC) and quality criteria. After confirming the model appropriateness, this global paediatric model was applied to the sparse PK data in children

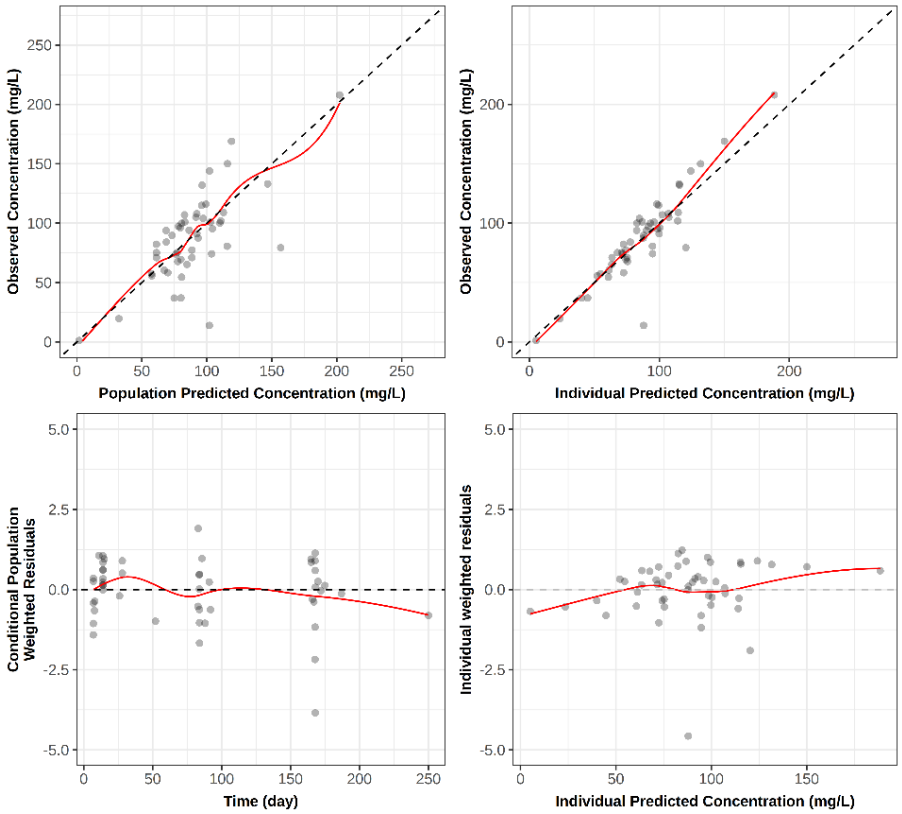
≥2 to <12 years of age with CSU through a MAP Bayesian approach by fixing all parameter estimates to the values from the global paediatric model. The individual PK parameters and exposure estimates for children with CSU were generated by MAP estimation with time-varying body weight covariate in children ≥2 to <12 years of age.

Figure 3. Visual predictive checks for global paediatric Pop PK model in children ≥2 to <12 years of age with CSU



Legend: blue dots: observations; blue solid and dashed lines: the median and bounds (5th and 95th percentiles) of observed concentrations at each time bin; red solid and dashed lines: the median and bounds (5th and 95th percentiles) of predicted concentrations at each time bin; pink and light blue areas: confidence intervals of median and percentiles of predicted concentrations at each time bin.

Figure 4. Goodness-of-fit plots for applying global paediatric Pop PK model in children ≥2 to <12 years of age with CSU



3. Paediatric CSU study PKM16982

Study PKM16982 was a multi-center, single-arm study to investigate the pharmacokinetics and safety of dupilumab in male and female participants ≥2 years to <12 years of age with uncontrolled chronic spontaneous urticaria (CSU).

Dupilumab was to be administered at doses defined by age and weight-tier for children (≥2 to <12 years) q2w or q4w. A total of 15 participants received dupilumab.

Dupilumab concentrations were measured using sparse sampling. Children ≥2 to <12 years of age with CSU were randomized 1:1 to PK schedule A (Weeks 0, 1, 12, 24, 36) or to PK schedule B (Weeks 0, 2, 12, 24, 36).

PK outcomes

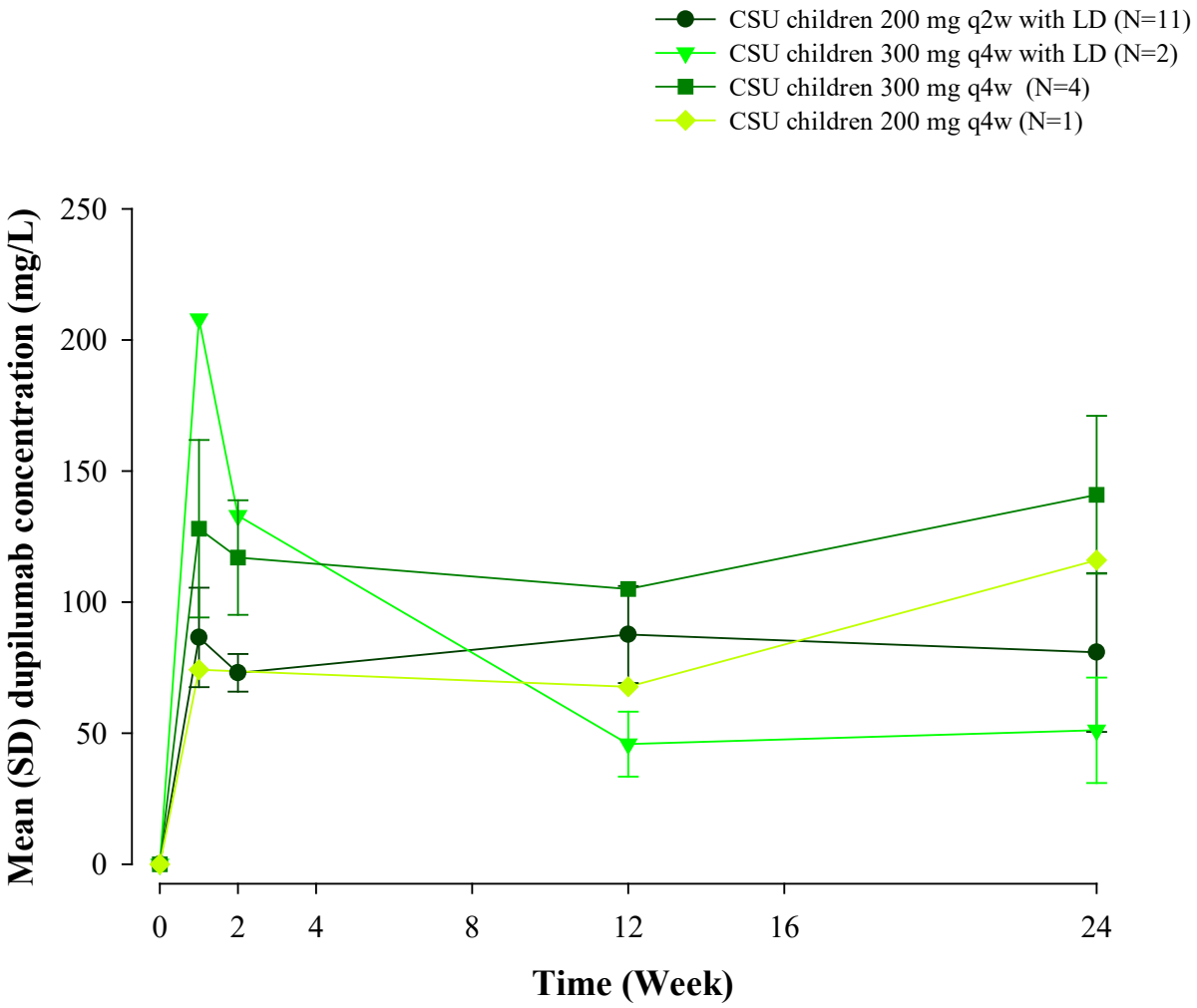
Following repeated administration of dupilumab in this study, the mean trough concentration of functional dupilumab in general increased during the treatment period, then decreased after cessation of dupilumab treatment during the study follow-up period. At Week 24, the mean concentration was 90.6 mg/L.

- Following administration of 200 mg q4w without a loading dose in a participant with **body weight ≥5 kg and <15 kg**, dupilumab Ctrough was 67.7 mg/L at Week 12 and 116 mg/L at Week 24.

- In participants with **body weight ≥15 kg and <30 kg** who received dupilumab 300 mg q4w with or without a 600 mg loading dose, mean (SD) dupilumab Ctrough was 65.5 (35.3) mg/L at Week 12 and 105 (54.4) mg/L at Week 24.
- In participants with **body weight ≥30 kg and <60 kg** who received dupilumab 200 mg q2w with a 400 mg loading dose, mean (SD) dupilumab Ctrough was 86.7 (19.8) mg/L at Week 12 and 78.5 (31.6) mg/L at Week 24.

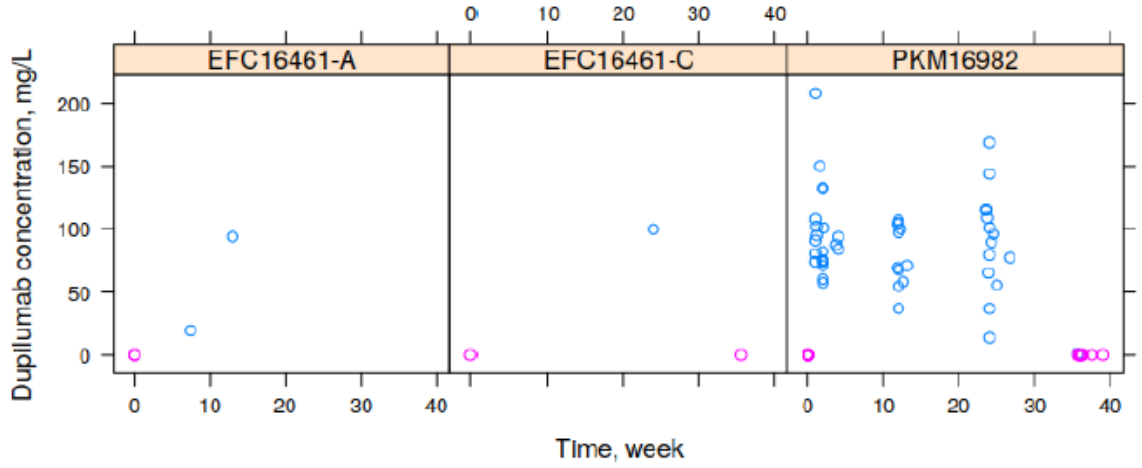
In all participants with the EOS results (data cut-off date of 14 November 2024), dupilumab concentration was <LLOQ (<0.078 mg/L) except one participant who received 300 mg q4w without a 600 mg loading dose.

Figure 5. Mean (±SD) concentrations of dupilumab in serum versus time in children ≥2 to <12 years of age by treatment group (Study PKM16982 and EFC16461 Study A and Study C)



BW: body weight; LD: loading dose; n: number of study participants; q2w: once every 2 weeks; q4w: once every 4 weeks.
In this plot (PKM16982 and EFC16461 Study A and Study C):
BW ≥30 to <60 kg, 200 mg q2w, and with LD: n=11.
BW ≥15 to <30 kg, 300 mg q4w, with LD, and ≥6 to <12 years of age: n=2.
BW ≥15 to <30 kg, 300 mg q4w, and ≥2 to <6 years of age: n=4.
BW ≥5 to <15 kg, 200 mg q4w: n=1.
Source: 5.3.5.2 PKM16982, Appendix 16.2.5 [16.2.5.4.2.2.1] of the current submission and 5.3.5.1 EFC16461 Study A and Study C, Appendix 16.2.5 [16.2.5.4.2.2.1] in previously submitted marketing application

Figure 6. Scatter plots of dupilumab concentrations versus time in children ≥2 to < 12 years of age with CSU by study



Notes: The pink dots represent the occurrences of concentration below the lower limit of quantitation (BLQ) at their corresponding time.

4. Population PK (popPK): Exposure estimates in children with CSU

After confirming the appropriateness of the afore global paediatric popPK model with MAP approach (ie, external validation using data from children with CSU), the global paediatric popPK model was used to generate post hoc estimates of individual steady-state exposures for each paediatric patient with CSU.

Table 6. Comparison of post hoc exposure estimated based on final global paediatric Pop PK models in children 6 months to <12 years of age with AD, asthma and EoE and final asthma paediatric model in children 6 to <12 years of age with asthma (POH1231)

Intrinsic/ extrinsic factors	Group		Predicted				Observed	
		N[a] (mean weight)	$AUCT_{,ss}$[b] (mg.day/L)	$AUC_{4week,ss}$[b] (mg.day/L)	$C_{max,ss}$[b] (mg/L)	$C_{trough,ss}$[b] (mg/L)	N[a] (mean weight)	$C_{trough,ss}$[b] (mg/L)
Post hoc PK exposures based on global paediatric Pop PK model								
Dosing Regimen	**200 mg q2w with LD**	10 (37.3 kg)	1760 (215)	3520 (430)	150 (17)	98.7 (13.3)	9 (37.8 kg)	80.9 (30.4)c
	300 mg q4w with LD	2 (25.7 kg)	2810 (362)	2810 (362)	162 (14)	55.6 (11)	2 (25.7 kg)	51.1 (20.1)c
	300 mg q4w	3 (19.1 kg)	5720 (1070)	5720 (1070)	289 (50.9)	138 (27.9)	3 (19.1 kg)	141 (30.1)c
	200 mg q4w	1 (14.5 kg)	4070	4070	204	99.2	1 (14.5 kg)	116c
Total		16 (31.0 kg)	--	3870 (1090)	181 (60)	101 (27.8)	15 (30.9 kg)	91.2 (39.4)

Abbreviation: AUCT,ss: area under the concentration time curve from time 0 to τ at steady state; AUC4week,ss: area under the concentration time curve from time 0 to 28 days at steady state; Cmax,ss: maximum concentration at steady state; Ctrough,ss: trough concentration at steady state; N: subject number; q2w: every two weeks; q4w: every four weeks; SD: standard deviation.
a. Due to dose discontinuation, one patient (last dose on Day 28) in study EFC16461 Study A and one patient (last dose on Day 1) in PKM16982 were excluded in this post assessment. One patient (last dose on Day 70) in EFC16461 Study A was included in this summary of post hoc steady-state PK exposures, as PK at 200 mg q2w with LD reached steady state at week 10 (based on simulation).

b. For 200 mg q2w, AUCτ,ss = AUC[week 22 – week 24], AUC4week,ss = AUCτ,ss x 2 and Cmax,ss and Ctrough,ss were calculated over Week 22 and Week 24. For 200 mg q4w and 300 mg q4w, AUCτ,ss = AUC[week 20 – week 24] =AUC4week,ss and Cmax,ss and Ctrough,ss were calculated over Week 20 and Week 24.
c. By the clinical database lock dates for PKM16982 (16 December 2024), 15 children had observed PK data at Week 24 in POH1231 dataset and were summarized in this table

5. PopPK model-based simulations

Model-based predictions in virtual paediatric population, which are not dependent on small N in each subgroup, represent a more accurate assessment of PK exposures of the weight-tiered dupilumab regimen studied children ≥2 to <12 years of age with CSU. PopPK simulations using virtual paediatric population from NHANES based on the paediatric popPK model were conducted for children ≥2 to <12 years of age (N = 2114).

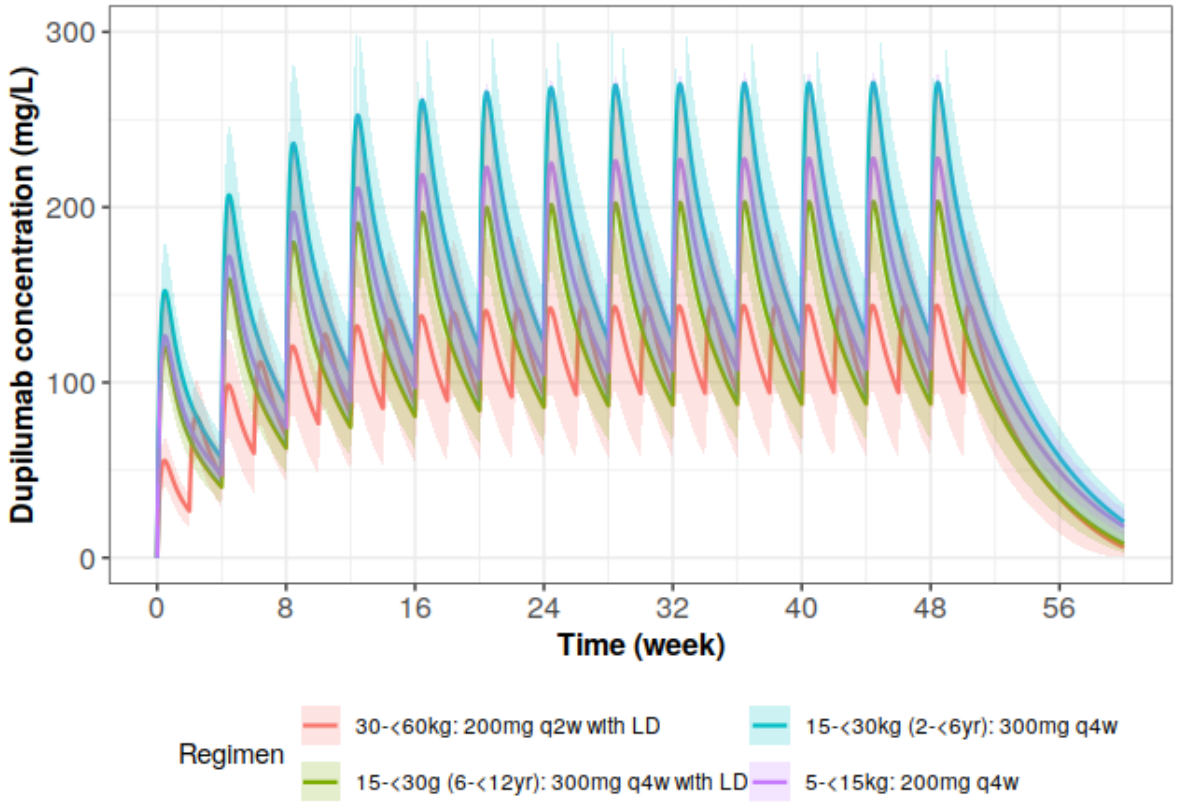
The correlation between baseline albumin and weight was minimal (r < 0.1) in the pooled paediatric dataset (1019 patients aged ≥2 to <12 years with AD, asthma, and EoE). Consequently, baseline albumin values for the virtual paediatric population (N = 2,114) were randomly assigned to replicate the distribution observed in the pooled dataset, ensuring comparable median, minimum, and maximum albumin values across both populations. The ADA status for the virtual paediatric population was assumed to be negative.

Table 7. Descriptive statistics of weight and age for virtual paediatric population from NHANES by weight and age group

Demographics	Weigt and age group	Dosing regimen	Virtual patients		
			N	Mean (SD)	Median (min – max)
Weight (kg)	30 to <60 kg	200 mg q2w with LD	667	40.4 (7.99)	38.5 (30.0, 59.8)
	15 to <30 kg (≥6 to <12 years)	300 mg q4w with LD	546	24.6 (3.26)	24.6 (16.4, 29.9)
	15 to <30 kg (≥2 to <6 years)	300 mg q4w	572	18.6 (2.89)	18.0 (150., 29.2)
	5 to <15 kg	200 mg q4w	329	13.2 (1.21)	13.4 (9.60, 14.9)
Age (Year)	30 to <60 kg	200 mg q2w with LD	667	9.2 (1.57)	9 (3, 11)
	15 to <30 kg (≥6 to <12 years)	300 mg q4w with LD	546	7.2 (1.23)	7 (6, 11)
	15 to <30 kg (≥2 to <6 years)	300 mg q4w	572	3.8 (0.996)	4 (2, 5)
	5 to <15 kg	200 mg q4w	329	2.4 (0.664)	2 (2, 5)

Abbreviations: LD: loading dose; q2w: every two weeks; q4w: every four weeks.

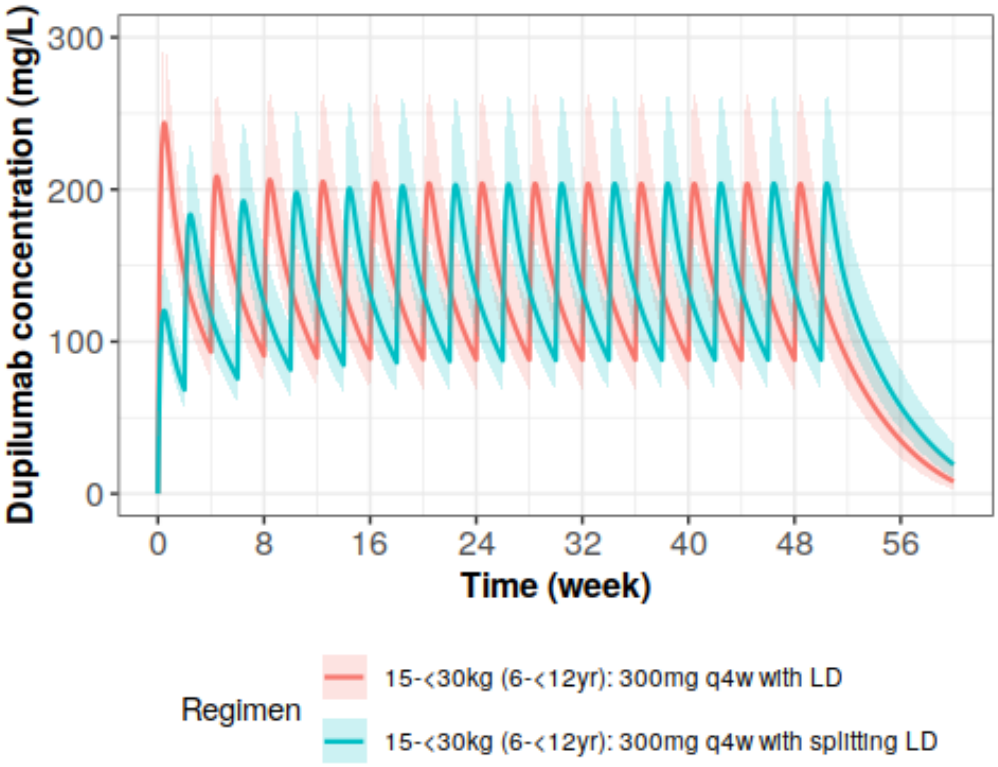
Figure 7. Simulated median (90% CI) concentration-time profiles in children ≥2 to <12 years of age with CSU by dosing regimen



Abbreviation: LD: loading dose; q2w: every two weeks; q4w: every four weeks.
Note: Median PK profile with 5th-95th percentile was simulated using global paediatric Pop PK models in children ≥2 to <12 years of age with body weight from 5 kg to 60 kg (N=2114, virtual paediatric population from NHANES). The median body weight was 38.5 kg for children with body weight ≥30 kg and <60 kg (200 mg q2w with LD, N=667), 24.6 kg for body weight ≥15 kg and <30 kg and age ≥6 to <12 years (300 mg q4w with LD, N=546), 18.0 kg for children with body weight ≥15 kg and <30 kg and age ≥6 to <12 years (300 mg q4w, N=572), and 13.4 kg for children with body weight ≥30 kg and <60 kg (for 200 mg q4w, N=329).

While the 600 mg loading dose was studied in children with AD aged ≥6 to <12 years with body weight ≥15 kg and <60 kg, a 'split' loading dose 300 mg on Day 1 followed by a second 300 mg on Day 15, then 300 mg q4w starting 4 weeks after Day 15 was agreed with CHMP/EMA during review of the variation to add this population with AD (See EPAR EMEA/H/C/004390/II/0027). PK simulations were submitted to support the split loading dose, and the relevant simulations have been reproduced.

Figure 8. Simulated median (90% CI) concentration-time profiles at 300 mg q4w with LD or split LD in children ≥6 to <12 years of age and ≥15 to <30 kg of weight with CSU



Abbreviation: LD: loading dose; q4w: every four weeks.
Split LD: first dose of 300 mg on Day 1, second dose of 300 mg on Day 15, and 300 q4w starting on Day 15.
Note: Median PK profile with 5th-95th percentile was simulated using global paediatric Pop PK models in children ≥6 to <12 years of age with body weight ≥15 kg and <30 kg (N=546, virtual paediatric population from NHANES). The median body weight was 24.6 kg for children ≥6 to <12 years of age with body weight ≥15 kg and <30 kg (300 mg q4w with LD or with split LD, N=546).

Table 8. Summary of simulated steady-state exposures (at Week 24) for dupilumab in children ≥2 to <12 years of age using virtual paediatric population from NHANES

Regimen	N	Median weight (kg)	$AUC_{T,ss}$ [a] (mg.day/L)		$AUC_{4week,ss}$ [a] (mg.day/L)		$C_{max,ss}$ [a] (mg/L)		$C_{trough,ss}$ [a] (mg/L)	
			Mean (SD) [CV%]	Median [P5-P95]	Mean (SD) [CV%]	Median [P5-P95]	Mean (SD) [CV%]	Median [P5-P95]	Mean (SD) [CV%]	Median [P5-P95]
30 to <60 kg: 200 mg q2w with LD	667	38.5	1640 (350) [21.3]	1660 [1070-2180]	3280 (696) [21.2]	3310 [2140-4350]	140 (28.3) [20.2]	142 [93.9-184]	90.9 (21) [23.1]	92 [56.5-123]
15 to <30 kg (≥6 to <12 years): 300 mg q4w with LD	546	24.6	3880 (614) [15.9]	3800 [3030-5090]	3880 (614) [15.9]	3800 [3030-5090]	203 (29.4) [14.4]	200 [163-261]	87.9 (16) [18.2]	85.9 [66.1-120]
15 to <30 kg (≥2 to <6 years): 300 mg q4w	572	18.0	5150 (758) [14.7]	5190 [3840-6290]	5150 (758) [14.7]	5190 [3840-6290]	264 (36.1) [13.7]	266 [202-318]	122 (19.9) [16.4]	123 [87-152]
5 to <15 kg: 200 mg q4w	329	13.4	4480 (493) [11]	4380 [3840-5390]	4480 (493) [11]	4380 [3840-5390]	228 (23.3) [10.2]	223 [197-270]	107 (13.1) [12.2]	105 [90.2-131]
15 to <30 kg (≥6 to <12 years): 300 mg q4w with splitting LD	546	24.6	3930 (611) [15.6]	3860 [3100-5080]	3930 (611) [15.6]	3860 [3100-5080]	206 (29.2) [14.2]	203 [166-261]	88.9 (15.9) [17.9]	87.2 [67.5-119]

Abbreviation: LD: loading dose; q2w: every two weeks; q4w: every four weeks; Split LD: first dose of 300 mg on Day 1, second dose of 300 mg on Day 15, and 300 q4w starting on Day 15.

Note: Steady-state PK exposures of dupilumab was simulated in children ≥2 to <12 years of age with body weight from 5kg to 60kg (N=2114, virtual paediatric population from NHANES) using global paediatric Pop PK models.

a. For 200 mg q2w, $AUC_{T,ss}$ = AUC[week 22 – week 24], $AUC_{4week,ss} = AUC_{T,ss} \times 2$ and $C_{max,ss}$ and $C_{trough,ss}$ were calculated over Week 22 and Week 24. For 200 mg q4w and 300 mg q4w, $AUC_{T,ss}$ = AUC[week 20 – week 24], $AUC_{4week,ss} = AUC_{T,ss}$ and $C_{max,ss}$ and $C_{trough,ss}$ were calculated over Week 20 and Week 24.

Table 9. Summary of simulated exposures after first dose for dupilumab in children ≥2 to <12 years of age using virtual paediatric population from NHANES

Regimen	N	Median weight (kg)	AUCT,s[a] (mg.day/L)		AUC_{4week}[a] (mg.day/L)		C_{max}[a] (mg/L)		C_{trough}[a] (mg/L)	
			Mean (SD) [CV%]	Median [P5-P95]	Mean (SD) [CV%]	Median [P5-P95]	Mean (SD) [CV%]	Median [P5-P95]	Mean (SD) [CV%]	Median [P5-P95]
30 to <60 kg: 200 mg q2w with LD	667	38.5	1180 (193) [16.4]	1190 [864-1470]	2460 (426) [17.3]	2480 [1760-3110]	113 (17.4) [15.4]	114 [84.6-139]	61.5 (11.5) [18.7]	62.1 [42.7-79.1]
15 to <30 kg (≥6 to <12 years): 300 mg q4w with LD	546	24.6	4300 (555) [12.9]	4240 [3520-5380]	4300 (555) [12.9]	4240 [3520-5380]	246 (29.4) [11.9]	243 [205-304]	94.9 (14.1) [14.9]	93.1 [75.2-123]
15 to <30 kg (≥2 to <6 years): 300 mg q4w	572	18.0	2620 (342) [13]	2640 [2040-3150]	2620 (342) [13]	2640 [2040-3150]	152 (17.9) [11.8]	152 [121-179]	56.2 (8.87) [15.8]	56.8 [40.9-69.5]
5 to <15 kg: 200 mg q4w	329	13.4	2240 (218) [9.74]	2200 [1950-2640]	2240 (218) [9.74]	2200 [1950-2640]	129 (11.4) [8.85]	126 [113-150]	48.4 (5.67) [11.7]	47.3 [41-58.8]
15 to <30 kg (≥6 to <12 years): 300 mg q4w with splitting LD	546	24.6	3410 (433) [12.7]	3360 [2810-4210]	3410 (433) [12.7]	3360 [2810-4210]	122 (14.4) [11.8]	120 [102-149]	69.4 (9.55) [13.8]	68.4 [56.3-87.2]

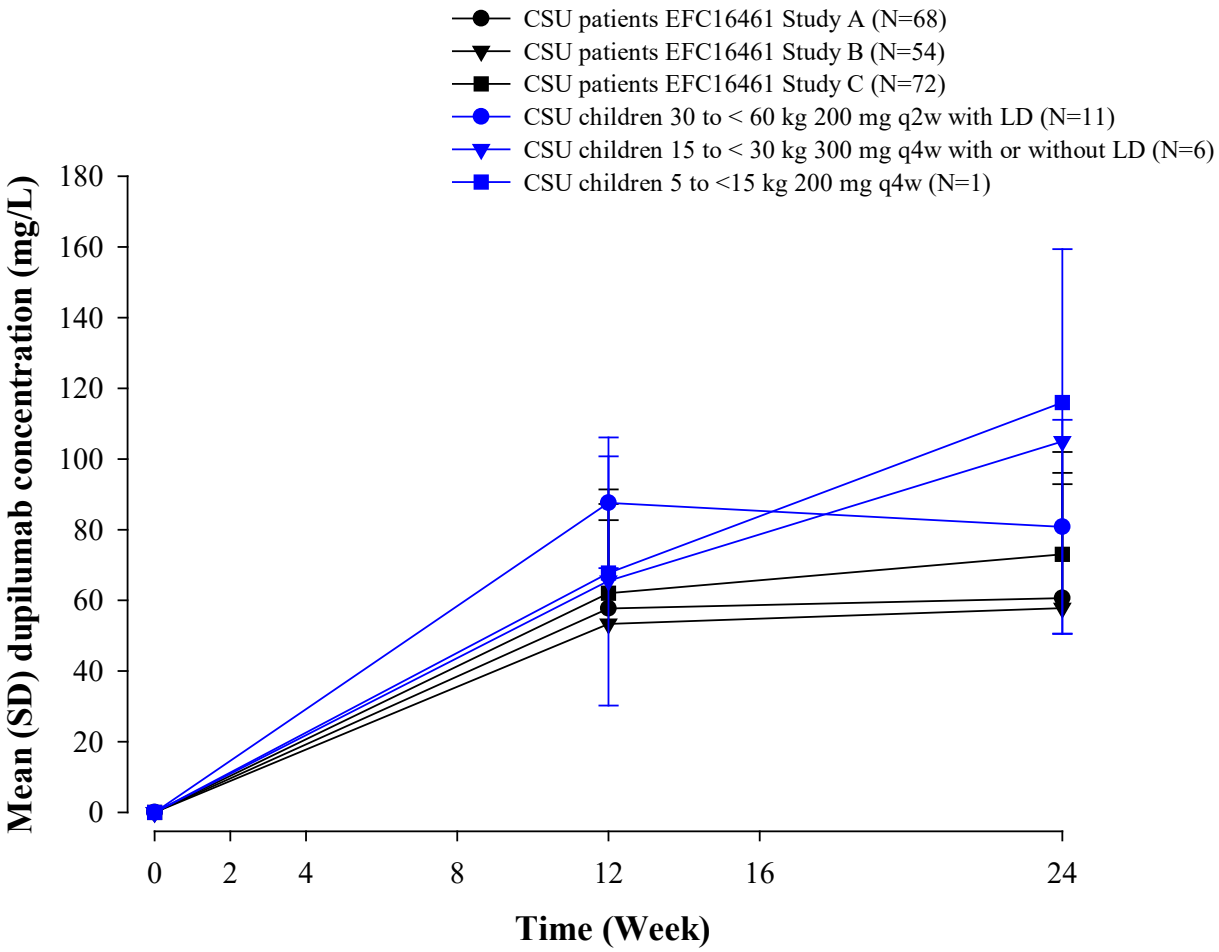
Abbreviation: LD: loading dose; q2w: every two weeks; q4w: every four weeks; Split LD: first dose of 300 mg on Day 1, second dose of 300 mg on Day 15, and 300 q4w starting on Day 15.

Note: Steady-state PK exposures of dupilumab was simulated in children ≥2 to <12 years of age with body weight from 5kg to 60kg (N=2114, virtual paediatric population from NHANES) using global paediatric Pop PK models.

a. For 200 mg q2w, $AUC_{T,s}$ = AUC[week 0 – week 2], AUC4weeks = AUC_T x 2 and Cmax and Ctrough were calculated over Week 0 and Week 2. For 200 mg q4w and 300 mg q4w, AUC_T = AUC[week 0 - week 4], AUC4week = AUC_T and Cmax and Ctrough were calculated over Week 0 and Week 4.

6. PK comparison between adults and children with CSU

Figure 9. Mean (±SD) trough concentrations of dupilumab in serum versus time in children ≥2 to <12 years of age, adolescents, and adults with CSU, by age, treatment, and body weight group



BW: body weight; LD: loading dose; N or n = number of participants; q2w: once every 2 weeks; q4w: once every 4 weeks.
In this plot (Study PKM16982 and EFC16461 Study A and Study C):
BW ≥30 to <60 kg, 200 mg q2w, with (w) LD: N=11.
300 mg q4w pooled, N=6: BW ≥15 to <30 kg, 300 mg q4w, w LD, and ≥6 to <12 years of age, n=2 pooled with BW ≥15 to <30 kg, 300 mg q4w, and ≥2 to <6 years of age, n=4.
BW: ≥5 to <15 kg, 200 mg q4w: N=1.

7. PK comparison across indications

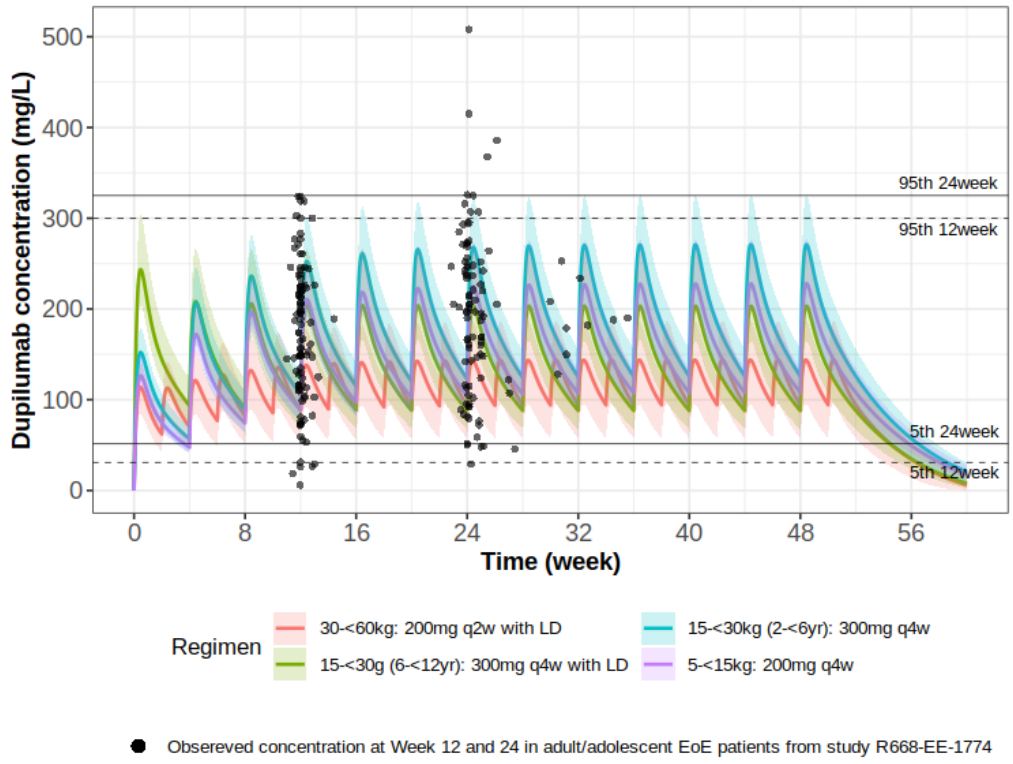
Table 10. Mean (SD) observed steady state exposure of dupilumab in children <12 years of age with CSU, AD, asthma, and EoE

Population	Age/Weight group	Study identifier	Dose*	$C_{trough,ss}$ (SD) (mg/L)	
				N	Observed*a*
CSU	2 to <12 years ≥30 to <60 kg	PKM16982, EFC16461 Study A and Study C	200 mg q2w with LD	9	80.9 (30.4)
	2 to <12 years ≥15 to <30 kg		300 mg q4w with or without LD	5	105 (54.4)
	2 to <12 years ≥5 to <15 kg		200 mg q4w	1	116
AD	6 to <12 years, ≥30 kg	R668-AD-1652	200 mg q2w with LD	52	86.0 (34.6)
	6 to <12 years, <30 kg		300 mg q4w with LD	57	98.7(33.2)
	6 months to <6 years ≥15 to <30 kg	R668-AD-1539 Part B	300 mg q4w	51	110 (42.8)
	6 months to <6 years ≥5 to <15 kg		200 mg q4w	24	109 (50.8)
Asthma	6 to <12 years >30 kg	EFC14153	200 mg q2w	158	90.4 (40.3)
	6 to <12 years ≤30 kg		100 mg q2w*b*	89	60.5 (26.5)
EoE	1 to <12 years, ≥30 to <60 kg	R668-EE-1877 Part A	200 mg q2w	7	89.8 (29.7)
	1 to <12 years, ≥15 to <30 kg		300 mg q4w	16	85.2 (29.6)
	1 to <12 years, ≥5 to <15 kg		200 mg q4w	4	81.4 (36.6)

*Dose: studied dose regimens in CSU and EoE paediatric population; approved dose regimens in AD (globally except the EU and EU-reference countries) and asthma paediatric populations
AD: atopic dermatitis; CSU: chronic spontaneous urticaria; $C_{trough,ss}$: trough concentration at steady state; EoE: eosinophilic esophagitis; N: number of patients; q2w: once every 2 weeks; SD: standard deviation
a The observed $C_{trough,ss}$ at Week 24 in CSU and asthma population, at Week 16 in AD and EoE population.
b 100 mg dose strength was discontinued and the associated 100 mg q2w posology was withdrawn

For children ≥2 to <12 years of age with CSU, Cmax was targeted not to exceed the Cmax associated with the highest dose regimen studied across indications (300 mg QW regimen, the approved dose in adult and paediatric patients ≥40 kg with EoE). The PopPK simulations of median (90% CI) concentration time profiles overlaid with observed individual concentrations of 300 mg QW (the highest tested regimen) in adults/adolescents with EoE (R668-EE-1774 Part A and Part B) are presented below. Furthermore, summary statistics of steady-state exposure predictions of dupilumab in adults/adolescents ≥40 kg with EoE are presented for comparison.

Figure 10. Simulated median (90% CI) concentration-time profiles in children ≥2 to <12 years of age with CSU by dosing regimen overlaid by observed trough concentration in adults/adolescents with EoE at dose 300 mg qw (linear scale)



Abbreviation: CSU: Chronic spontaneous urticaria; EoE: eosinophilic esophagitis; LD: loading dose; qw: every week; q2w: every two weeks; q4w: every four weeks.
Note: Colored curves and shaded regions: Median PK profile with 5th-95th percentile was simulated using global pediatric Pop PK model in children ≥2 to <12 years of age with body weight from 5 kg to 60 kg (N=2114, virtual pediatric population from NHANES). The median body weight was 38.5 kg for children with body weight ≥30 kg and <60 kg (200 mg q2w with LD, N=667), 24.6 kg for body weight ≥15 kg and <30 kg and age ≥6 to <12 years (300 mg q4w with LD, N=546), 18.0 kg for children with body weight ≥15 kg and <30 kg and age ≥2 to <6 years (300 mg q4w, N=572), and 13.4 kg for children with body weight ≥5 kg and <15 kg (for 200 mg q4w, N=329).
Points: observed trough concentrations at Week 12 and 24 at 300 mg qw in EoE adult and adolescent patients from study R668-EE-1774 Part A and Part B.
Horizontal lines: 5th and 95th percentiles of observed concentrations at Week 12 (dash) and Week 24 (solid) at 300 mg qw in adult and adolescent EoE patients from study R668-EE-1774 Part A and Part B.

Table 11. Summary Statistics of Steady-State Exposure Predictions of Dupilumab by Weight-Tiered Dose Regimen in Adults and Adolescents ≥40 kg with EoE, Median (P5, P95)

Dose and Weight	Group	$AUC_{4wks,ss}$ (mg*d/L)	$AUC_{tau,ss}$ (mg*d/L)	$C_{max,ss}$ (mg/L)	$C_{trough,ss}$ (mg/L)
300 mg QW, ≥40 kg	Adults and adolescents ≥12 years	6074 (3404, 10951)	1518 (851, 2738)	222 (126, 396)	207 (113, 383)

Abbreviations: AUC=area under the concentration-time curve; AUC4wks,ss=AUC at steady-state over 4 weeks; AUCτau,ss=AUC at steady-state over the dosing interval; Cmax,ss=maximum concentration within the steady-state dosing interval; Ctrough,ss=concentration at the end of steady-state dosing interval; P5=5th percentile; P95=95th percentile; QW=once weekly.
Note: There were 1000 simulated participants in each group in this table.

2.3.3. Pharmacodynamics

Mechanism of action

Through inhibition of IL 4 and IL 13 signaling via binding to the IL 4Rα subunit shared by the IL 4 and IL 13 receptor complexes and potential to block IgE-dependent and IgE-independent pathways, dupilumab may provide a new therapeutic approach for the treatment moderate-to-severe CSU in patients 2 years and older, whose disease is not adequately controlled with H1-antihistamine and who are naïve to anti-IgE therapy for CSU.

Primary and secondary pharmacology

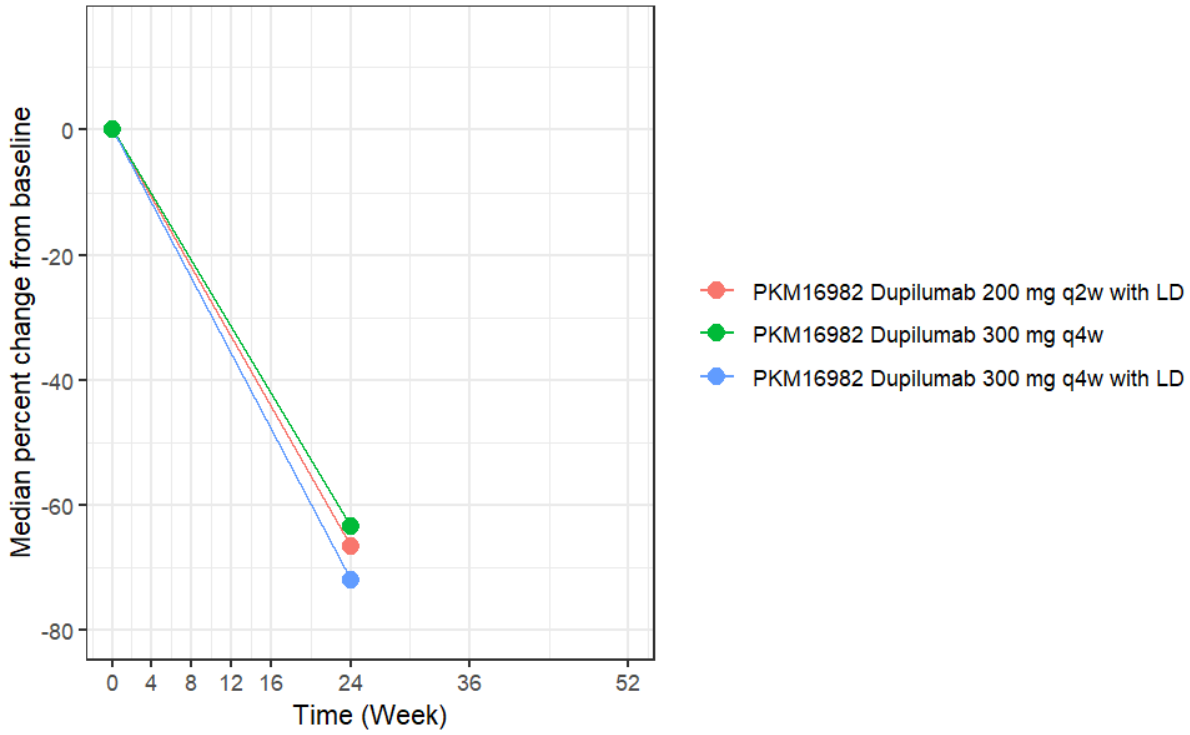
At the tie of this procedure, there is no available validated CSU specific biomarker which can be used for disease activity evaluation or for treatment effect assessment. Total IgE was evaluated in the CSU development program to better understand and further characterize dupilumab's mode of action in CSU.

Concentrations of total IgE in serum were measured using a validated quantitative method: a fluoroenzyme immunoassay was used globally while a comparable electrochemiluminescence immunoassay was used in China.

In study PKM16982, total-IgE serum samples were collected at baseline and on-treatment at Week 24.

Figure 11. Median percent change in total IgE in serum over time following dupilumab in children with CSU

Children ≥2 to <12 years of age (Study PKM16982)*a*



CSU: chronic spontaneous urticaria; EOS: end of study; EOT: end of treatment; IgE: immunoglobulin E; N: number of study participants; q2w: once every 2 weeks; q4w: once every 4 weeks; SD: standard deviation.
a PKM16982: dupilumab 200 mg q4w, N =0; dupilumab 300 mg q4w, N=3; dupilumab 300 mg q4w with a loading dose, N=2; dupilumab 200 mg q2w with a loading dose, N=8; EOT = 24 weeks; EOS = 36 weeks. The figure shows the on-treatment data for PKM16982.

In EFC16461 Study A and Study C, concentrations of total IgE in serum in children with CSU showed a decline during the dupilumab treatment period and were within the range of the individual change in adults with CSU at the corresponding time points.

The total IgE profiles showed a similar median magnitude of effect over time in children <12 years of age with CSU, asthma, and EoE.

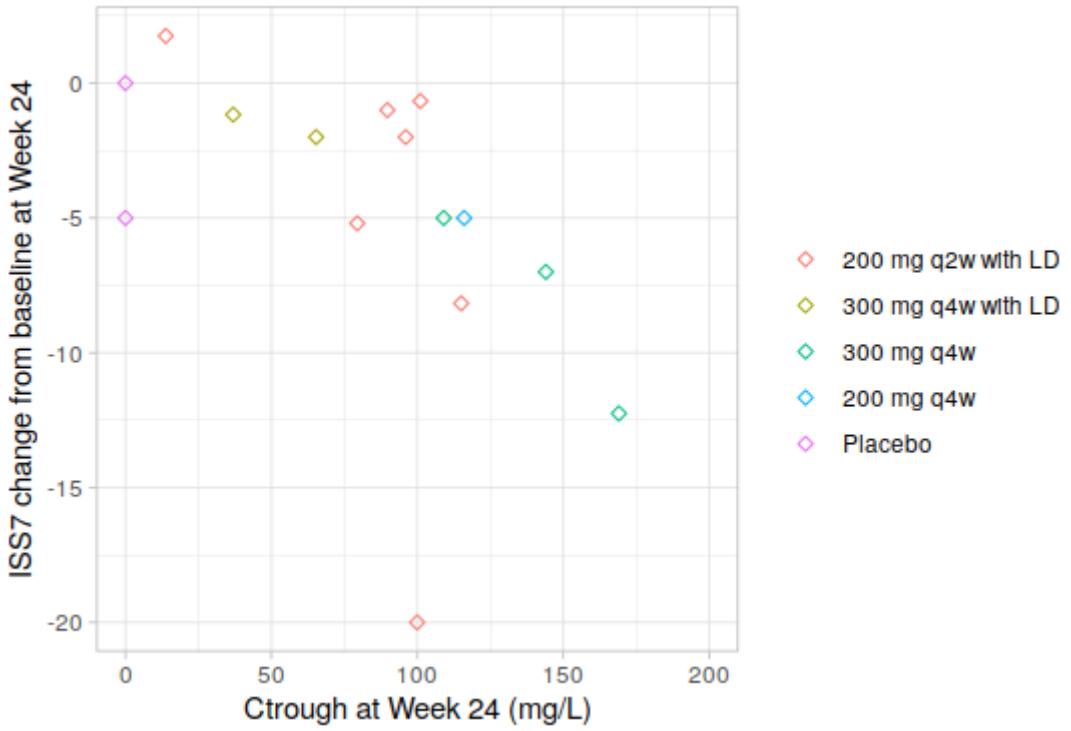
2.3.4. PK/PD modelling

A descriptive exposure-efficacy analysis by dupilumab Ctrough subgroups (low [<median] and high [≥median]) in children ≥2 to <12 years of age with CSU was conducted to examine the apparent correlation of the response with the trough concentrations of dupilumab.

As described previously, for the descriptive analysis in patients with CSU (adults, adolescents and children), the E-R relationship was explored by quartiles of steady-state trough concentration of dupilumab for the key efficacy endpoints UAS7, ISS7, and HSS7 at Week 24 with the data from study EFC16461.

Descriptive E-R analysis for ISS7

Figure 12. Scatter plot of ISS7 change from baseline versus observed C_{trough} (mg/L) at Week 24 in children ≥2 to <12 years of age with CSU (Study PKM16982 and EFC16461 Study A and Study C)



C_{trough}: minimum concentration; ISS7: itch severity score over 7 days; LD: loading dose; q2w: once every 2 weeks; q4w: once every 4 weeks.
In this plot, total subject number was 15: 200 mg q2w with LD for children with body weight (at baseline) ≥30 to <60 kg (N=7); 300 mg q4w with LD for children with body weight ≥15 to <30 kg and ≥6 to <12 years of age (N=2); 300 mg q4w for children with body weight ≥15 to <30 kg and ≥2 to <6 years of age (N=3); 200 mg q4w for children with body weight ≥5 to <15 kg (N=1); placebo for children with body weight ≥30 to <60 kg (N=2). (PKM16982, EFC16461 Study A and Study C).
Due to dose discontinuation and missing trough concentration at Week 24, 3 participants in dupilumab treatment group (1 from PKM16982 and 2 from EFC16461 Study A) were excluded in the descriptive exposure response analysis at Week 24.
Due to missing efficacy data at Week 24, 2 participants in dupilumab treatment group from PKM16982 were excluded in the descriptive exposure response analysis.
The missing baseline ISS7 value in 1 participant from PMK16982 was imputed with ISS7 value on Day 1 for this participant in the descriptive exposure response analysis,
Last efficacy data for placebo patients (N=2) were collected at Week 22.

Table 12. ISS7 change from baseline by observed C_{trough} subgroup at Week 24 in patients with CSU in Studies PKM16982 and EFC16461 (Study A and Study C)

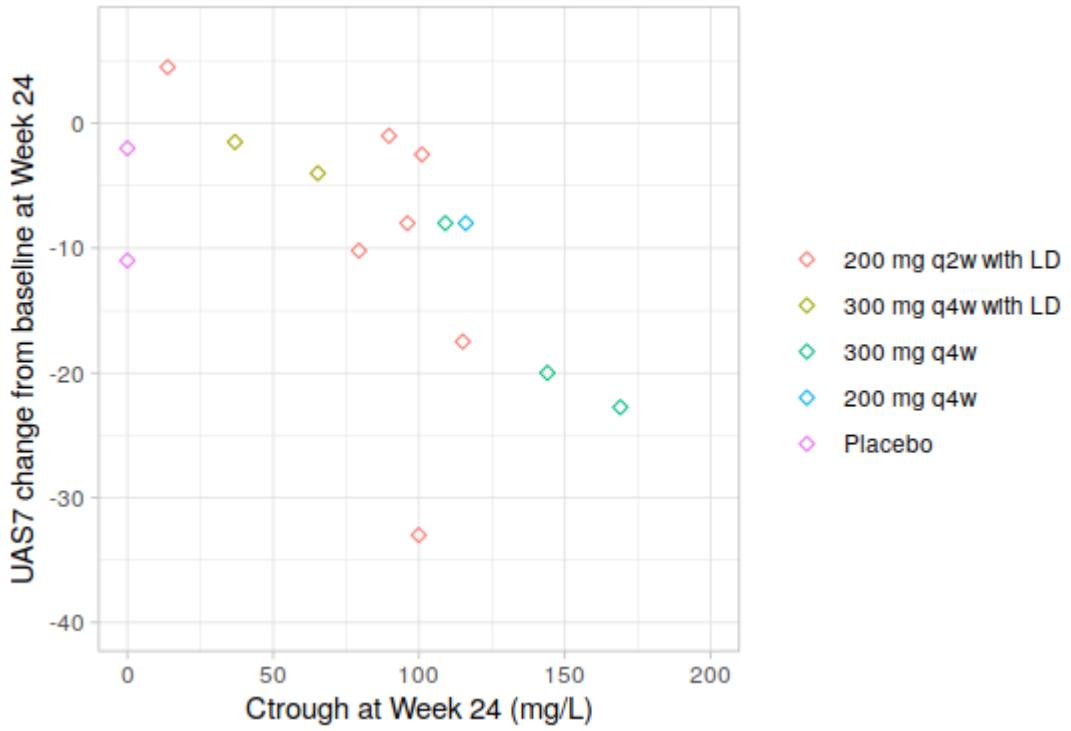
Study	C_{trough} subgroup	ISS7 change mean	ISS7 change standard error	C_{trough} mean (mg/L)	C_{trough} standard error	ISS7 BL Mean	H1-AH BL Dose % Standard dose	BL weight (kg)
PKM16982	Low	-4.23	2.74	68.7	12.3	12.0	NA	34.7
	High	-6.35	1.46	126	9.72	8.22	NA	24.0
EFC16461	Placebo	-6.1	0.6	0	NA	15.4	187%	74.0

Study	C_{trough} subgroup	ISS7 change mean	ISS7 change standard error	C_{trough} mean (mg/L)	C_{trough} standard error	ISS7 BL Mean	H1-AH BL Dose % Standard dose	BL weight (kg)
Study C +Study A	1	-8.8	1.2	27.0	2.9	15.5	193%	87.8
	2	-8.7	1.3	55.7	1.0	16.3	187%	81.1
	3	-10.6	1.1	77.1	1.3	15.7	182%	72.7
	4	-10.2	1.3	109.3	3.1	15.3	169%	59.9

BL: baseline; CSU: chronic spontaneous urticaria; C_{trough}: trough concentration; H1-AH: H1-antihistamine; ISS7: itch severity score over 7 days; N: number of study participants; NA: not applicable.
The total number of study participants for the descriptive exposure response analysis in children ≥2 to <12 years with CSU was N=13 (N=12 from Study PKM16982 and N=1 from EFC16461 Study C).
Due to lack of efficacy data at later week, 3 participants from study PKM16982 and 1 participant from EFC16461 Study A were excluded in this table.
One participant with missing baseline value of ISS7 was imputed with ISS7 value on Day 1 for this participant and included in this summary.
N=6-7 per group in PKM16982. Low < median C_{trough}; high ≥median C_{trough}
Quartile values: Q1 = 40.9; Q2 = 56.2; Q3 = 75.7 mg/L for dupilumab in Study A and Study C.
N=29 to 32 per quartile in Study A and Study C.

Descriptive E-R analysis for UAS7

Figure 13. Scatter plot of UAS7 change from baseline versus observed C_{trough} (mg/L) at Week 24 in children ≥2 to <12 years of age with CSU (Study PKM16982 and EFC16461 Study A and Study C)



C_{trough}: minimum concentration; LD: loading dose; N: number of study participants; q2w: once every 2 weeks; q4w: once every 4 weeks; UAS7: urticaria activity score over 7 days.
In this plot, total subject number was N=15: 200 mg q2w with LD for children with body weight (at baseline) ≥30 to <60 kg (N=7); 300 mg q4w with LD for children with body weight ≥15 to <30 kg and ≥6 to <12 years of age (N=2); 300 mg q4w for children with body weight ≥15 to <30 kg and ≥2 to <6 years of age (N=3); 200 mg q4w for children with body weight ≥5 to <15 kg (N=1); placebo for children with body weight ≥30 to <60 kg (N=2).
Due to dose discontinuation and missing trough concentration at Week 24, 3 participants in dupilumab treatment group (1 from Study PKM16982 and 2 from EFC16461 Study A) were excluded in the descriptive exposure response analysis at Week 24.
Due to missing efficacy data at Week 24, 2 participants in dupilumab treatment group from PKM16982 were excluded in the descriptive exposure response analysis.
The missing baseline UAS7 value in 1 participant from Study PKM16982 was imputed with UAS7 value on Day 1 for this participant in the descriptive exposure-response analysis.
Last efficacy data for placebo patients (N=2) were collected at Week 22.

Table 13. UAS7 change from baseline by observed C_{trough} subgroup at Week 24 in patients with CSU in Study PKM16982 and EFC16461 Study A and Study C

Study	C_{trough} subgroup	UAS7 change mean	UAS7 change standard error	C_{trough} mean (mg/L)	C_{trough} standard error	UAS7 BL Mean	H1-AH BL Dose mean	BL weight (kg)
PKM16982	Low	-7.60	4.61	68.7	12.3	21.5	NA	34.7
	High	-13.1	3.04	126	9.72	16.9	NA	24.0
EFC16461	Placebo	-11.7	1.2	0	NA	29.4	187%	74.0
Study C + Study A	1	-17.6	2.3	27.0	2.9	30.3	193%	87.8
	2	-16.3	2.5	55.7	1.0	30.9	187%	81.1
	3	-19.6	2.2	77.1	1.3	29.8	182%	72.7
	4	-19.4	2.5	109.3	3.1	28.7	169%	59.9

BL: baseline; CSU: chronic spontaneous urticaria; C_{trough}: trough concentration; H1-AH: H1-antihistamine; UAS7: urticaria activity score over 7 days; N: number of study participants; NA: not applicable.
The total subject number for the descriptive exposure response analysis in children ≥2 to <12 years with CSU was N=13: N=12 from Study PKM16982 and N=1 from EFC16461 Study C).
Due to lack of efficacy data at later week, 3 participants from study PKM16982 and 1 participant from EFC16461 Study A were excluded in this table.
One participant with missing baseline value of UAS7 was imputed with UAS7 value on Day 1 for this participant and included in this summary.
N = 6-7 per group in PKM16982; Low <median C_{trough}; High ≥median C_{trough}
Quartile values: Q1 = 40.9; Q2 = 56.2; Q3 = 75.7 mg/L for dupilumab in Study A and Study C;
N = 29 to 32 per quartile in Study A and Study C.

2.3.5. Immunogenicity

In study PKM16982, anti-drug-antibody serum samples were collected at baseline, on-treatment at Week 12 and Week 24, and follow-up at Week 36.

There were no participants with samples positive for ADA in Study PKM16982.

No positive ADA responses were observed in the children with CSU in EFC16461 Study A and Study C.

2.3.6. Discussion on clinical pharmacology

The applicant aims to extend the indication of Dupixent to CSU in children aged ≥2 to <12 years. The PK of dupilumab in serum has previously been described in adults and adolescents with CSU (procedure EMA/VR/0000257461) as well as in healthy subjects and in patients with AD, asthma, CRSwNP, EoE, PN, and COPD (approved indications).

The paediatric clinical development program for dupilumab in CSU in children aged ≥2 to <12 years was based on an extrapolation approach that was previously agreed by Paediatric Investigation Plan (see section 2.1.3.). The development plan consists of 3 studies with 24-week treatment duration:

- the PK and safety study PKM16982 included only paediatric patients (15 children aged ≥2 to <12 years);

- Master protocol EFC16461 comprised 2 independent Phase 3 studies that included 5 children aged ≥6 and <12 years along with adults and adolescents.

Dupilumab PK and response data in paediatric patients from 2 to less than 12 years from the 3 studies and supportive exposure-response data from adult / adolescent patients with CSU from EFC16461 Study A, B, and C were planned to be part of the extrapolation plan of efficacy from adults/ adolescents to the paediatric population. According to extrapolation plan, the PD endpoints in exposure-response analyses, including ISS7 and HSS7, should support the assumption that the exposure-response relationships at the selected doses are similar in children from 2 years to less than 12 years of age and in adult / adolescent patients with CSU.

A weight-banded dosing was applied in the studies that was guided by paediatric dose regimens already approved in other indications.

- Children with body weight ≥5 kg to <15 kg received 200 mg q4w (without a loading dose) irrespective of age. This dosage scheme is already approved for children 6 months to 5 years of age with AD.
- Children aged 2 to 5 years: 300 mg q4w (with no loading dose) in children with **body weight ≥15 kg to <30 kg**. This dosage scheme is already approved for children 6 months to 5 years of age with AD.
- Children aged 6 to 11 years:
    - 300 mg q4w (with a 600 mg loading dose) in children with **body weight ≥15 kg and <30 kg** is an approved dosage scheme in AD in this age group for body weight ≥15 to <60 kg with a split loading dose.
    - 200 mg q2w (with a 400 mg loading dose) in children with **body weight ≥30 kg to <60 kg** is approved in asthma in this age/weight group (however without loading dose).
    - 300 mg q2w with an initial 600 mg loading dose in children with **body weight ≥60 kg** is the approved adult CSU dose.

Previously established bioanalytical methods were applied to measure dupilumab exposure. Bioanalytical reports were provided and acceptable method performance was reported.

In the paediatric CSU study PKM16982, dupilumab concentrations were measured using sparse sampling (weeks 0, 1 or 2 (randomized 1:1), 12, 24, 36). The sample size in the different dosing groups was low, with only 1 patient aged 6 years, weighing 14.5 kg in the 200 mg q4w group. For this patient dupilumab C_{trough} was 116 mg/L at Week 24 and comparable to the 300 mg q4w dosing group (with or without a 600 mg loading dose; N=6)), where mean (SD) dupilumab C_{trough} was 105 (54.4) mg/L at Week 24. In the dosing group dupilumab 200 mg q2w with a 400 mg loading dose (N=8) the mean (SD) dupilumab C_{trough} at week 24 was lower (78.5 (31.6) mg/L).

Mean (±SD) trough concentrations of dupilumab at week 12 and week 24 in children ≥2 to <12 years of age vs. adolescents/ adults with CSU were graphically compared by presentation of concentration-time curves for each dosing group. It is worthwhile noting that chosen presentation is somewhat misleading as it includes pre-dose (week 0) and thus, indicates an increase in concentration up to week 12. As only trough samples were collected in study EFC16461, it should be noted that complete profiles can only be simulated for both, adult and paediatric population.

The target dupilumab exposure range for children with CSU was defined: In steady state, C_{trough} should be above 63.5 to 74.7 mg/L (mean C_{trough} in adults/adolescents with CSU) and Cmax should not

exceed 216 to 222 mg/L (mean Cmax in adults/adolescents with highest tested dosing regimen concluded to be safe). For assessment of Cmax, estimated values from the global paediatric popPK model need to be considered (see assessment below), as only sparse PK sampling was applied.

The observed mean trough concentrations obtained by the chosen dosing regimens in children with CSU were above 63.5 to 74.7 mg/L in all dosing groups at week 24, thus, above an exposure level proven to be efficacious. Simulated mean and median exposure are considered comparable.

Mean observed C_{trough} obtained in children with CSU was also compared to other indications by dosing group with higher number of patients for asthma, EoE and AD (paediatric populations). Overall, comparable dupilumab C_{trough} at week 24 was achieved across within the dosing groups. Differences between dosing groups were seen regardless of indication, with highest exposure in children <30 kg with CSU and AD. It is noted that the 116 mg/L obtained in the only CSU patient in the 200 mg q4w dosing group was higher than any presented mean C_{trough}.

Population PK analysis and modelling

Given that "indication" was not to found predictive for PK, a global paediatric popPK model was developed, based on all available information on paediatric PK from already approved indications. The global paediatric popPK model was based on 3748 PK concentrations from 1019 paediatric patients aged < 12 years old, 544 children with AD (aged ≥6 months to <12 years), 377 children with asthma (aged ≥6 to <12 years), and 98 children with EoE (aged ≥1 to <12 years). It is informed by six clinical studies (Phase 2 and 3) with PK data from children aged 6 months to 6 years of age where sparse and semi-dense PK data were collected. Semi dense data allowed the estimation of the absorption rate Ka. The inclusion of a paediatric-specific Ka (about 3 times higher to the adult one) is acknowledged.

Weight effects have been included in the base model, that is agreed based on prior knowledge of this effect on PK. The discrimination between time-varying over baseline weight effect was made based on the parameter estimation process and a sensitivity analysis. The Pop PK base model using time-varying weight reduced the objective function value significantly. Thus, the selection of time-varying effect over baseline weight effect is deemed plausible. The model estimating V2, Ke, Ka, IIV for V2 and Ke, and weight-effect exponents on V2 and Ke, with other parameters fixed to the global base model (including bioavailability after SC administration that is assumed to be 63% for all paediatric age groups and adults), was selected as the final paediatric base model due to precise parameter estimates and acceptable diagnostic performance, that was reported as well. The VPC plots provided for final global paediatric model stratified by disease, age group or study are of acceptable quality.

The final global paediatric Pop PK model was used for external validation to investigate whether dupilumab PK in 18 children ≥2 to <12 years of age with CSU from three clinical studies EFC16461 Study A (N=2), Study C (N=1), and PKM16982 (N=15) could be described. Following the provided visual predictive check plot and goodness-of-fit plots, it is agreed that overall, the global paediatric model is able to describe the observed data acceptably well.

The global paediatric popPK model was used to generate post hoc estimates of individual steady-state exposures for each paediatric patient with CSU. Furthermore, simulations.

Furthermore, Simulations were provided using virtual paediatric populations from US National Health and Nutrition Examination Survey (NHANES) for 2114 children ≥2 to <12 years of age. The database is deemed representative for the planned indication regarding body weights; the lowest body weight in this data base was 9.6 kg. Simulated median (90% CI) concentration-time profiles of these virtual patients were presented by dosing group.

PK model post hoc estimates of individual steady-state exposures (AUC, Cmax, Ctrough) for each paediatric patient with CSU were generated. Considering the different paediatric dosing regimens,

differences in exposure were seen with post hoc mean Cmax,ss 300 mg q4w (289 mg/L) > 200 mg q4w (204 mg/L) > 300 mg q4w with loading dose (162 mg/L) > 200 mg q2w with loading dose (150 mg/L). Thus, considering estimated mean values for children 2-5 years of age with 300 mg q4w dosing, the upper limit of the target exposure (216 to 222 mg/L) has been exceeded formally. Sample size was very low in these analyses (N=3), however, simulated mean Cmax using virtual paediatric population from NHANES (N=572) has also been estimated to be above the exposure target in this dosing group (264 mg/L). The applicant argues that the 95th percentile of Cmax at steady state achieved by the regimens of paediatric patients with CSU is lower than the 95th percentile of Cmax associated with the approved 300 mg QW regimen (318 vs 396 mg/mL), which is acknowledged. The simulated concentrations (C_{trough} and Cmax) in children with CSU are within the range of observed concentrations in adults/adolescents treated with the highest approved dosing regimen; few individuals had exposure up to approximately 500 mg/L.

In children ≥6 to <12 years of age with CSU, a loading dose was administered to achieve effective drug concentrations more rapidly. A similar approach was chosen for AD and is acceptable for CSU as well. However, a high initial dupilumab concentration was seen in the children receiving a 600 mg loading dose (300 mg q4w dosing group with body weight ≥15 kg and <30 kg, aged ≥6 to <12 years) that was also indicated by simulations of median Cmax using virtual demographic data from NHANES. The applicant thus proposes a split loading dose (300 mg on Day 1 followed by a second 300 mg on Day 15) in this age/weight group, although not being covered by study data. Simulated median (90% CI) concentration-time profiles indicated that the split loading dose resulted in a lowered peak concentration after initial dosing, while steady state concentrations were not affected. Splitting of the high loading dose in this age/weight group was agreed with CHMP during review of the paediatric data in the AD population and is also acceptable for the proposed CSU population.

PD response

To date there is no available validated CSU specific biomarker. Biomarker total IgE was evaluated in order to further characterize dupilumab's mode of action in CSU. In Study PKM16982, there was a decrease from baseline in total IgE at week 24 in all dosing groups presented (median percent change from baseline in serum IgE levels at Week 24 was 69.4%). Overall, results on IgE are considered supportive information only and do not raise concern.

Exposure response analysis

A descriptive exposure-efficacy analysis was conducted for children with CSU. UAS7, ISS7, and HSS7 at week 24 were analysed as efficacy measure; Ctrough at week 24 was used as exposure metrics and split in high (≥median Ctrough) and low (< median Ctrough). Considering the low number of patients, the splitting in 2 exposure subgroups only is deemed reasonable. Furthermore, given the low sample size, it is acceptable that results are not presented by dosing group (dose-exposure-response analysis). No placebo data are available for the 2 to 5-year-old group. Regarding ISS7, ISS7 mean change from baseline was -4.23 in the low exposure subgroup and -6.35 in the high exposure subgroup. Thus, a numerical difference was seen. However, the change from baseline in the higher exposure subgroup was in the range of placebo rate in adult study EFC16461 (-6.1), the change in the low exposure subgroup was even lower. Comparable results were obtained for efficacy endpoints UAS7 and HSS7 at week 24.

The Paediatric Investigation Plan states that PD endpoints in exposure-response analyses, including ISS7 and HSS7, should support the assumption that the exposure-response relationships at the selected doses are similar in children from 2 years to less than 12 years of age and in adult / adolescent patients with CSU. Although there is a tendency for numerically higher efficacy with higher exposure in both, adults/adolescents and children, a direct comparison of the 2 population is difficult

with data available. The baseline disease severity was lower in paediatric study PKM16982 as compared to study EFC16461 as children were included independent of disease severity at baseline. Furthermore, placebo rate in children with CSU is unknown and might differ from adult placebo rate. Overall, given the described uncertainties, the exposure-response analyses are not sufficient for a statement on similar exposure-response relationship in children vs adult / adolescent patients with CSU. While exposure-response data can be considered as supportive, assessment of appropriateness of the proposed dose regimens in children aged ≥2 to 11 years of age with CSU depends on exposure matching and simulation.

Immunogenicity

No positive ADA responses were observed in the children with CSU in studies PKM16982 and EFC16461 (Study A and Study C). Considering the limited available data with ADA samples up to week 36 following 24 weeks of treatment, the immunogenic potential in children with CSU seems to be low.

2.3.7. Conclusions on clinical pharmacology

A direct comparison of the exposure-response relationship between children and adult/adolescent patients is hampered by relevant uncertainties including uncontrolled study design with unknown placebo-rate in children, limited patient number (20 patients, with 18 treated with dupilumab and 2 with placebo), and less severe study population, and can be considered as supportive data only. Therefore, the extrapolation of efficacy in children aged ≥2 to 11 years of age with CSU weighing at least 5 kg is based on exposure matching. As PK observations in children with CSU are limited, prior PK knowledge from previously approved paediatric indications needs to be considered and a model-based simulation approach has been deemed of high impact for a credible description of PK in the paediatric target population. Given that "indication" was not to found predictive for dupilumab PK, a global paediatric popPK model was developed, based on all available paediatric PK data from previously approved paediatric indications (atopic dermatitis [AD], asthma, and eosinophilic esophagitis [EoE]) for dupilumab in children aged from 6 months to <12 years. This global paediatric popPK model describes the observed data in children with CSU acceptably well, and is deemed qualified to predict PK in paediatric CSU patients.

With resulting simulations, paediatric exposure of dupilumab is predicted to be near the upper limit of what has been established as safe in adults/adolescents. However, the dosing regimen resulting in highest predicted exposure is already approved in AD in the here proposed age group. It is therefore reassuring that no exposure-related increases in adverse events were identified in children with AD. Furthermore, the safety profile in the limited number of children with CSU did not deviate from the hitherto known safety profile in paediatric patients younger than 12 years using the same weight-banded dosing. Thus, it is agreed with the applicant that based on available data there is no indication that the higher exposure seen with the chosen paediatric dose regimens has an impact on dupilumab's safety profile.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose response study was performed.

2.4.2. Main studies

Data for clinical efficacy in paediatric participants with moderate-to-severe CSU whose disease is not adequately controlled with H1-antihistamine treatment are derived from the phase 3 studies (study

PKM16982 and EFC16461 Study A and Study C) that beside the inclusion of adults and adolescents also included participants aged 2 to <12 years old (see Table 1).

In addition to the PK data from children 2 to <12 years old (see Section 2.3.), the efficacy evaluation is based on extrapolation from adult and adolescent patients with CSU with the same line of treatment (moderate-to-severe disease inadequately controlled with H1 antihistamines and naïve to anti-IgE treatment; EMA/VR/0000257461) as similar disease pathology and response to dupilumab treatment is assumed between children and adolescents/adults in this CSU patient population.

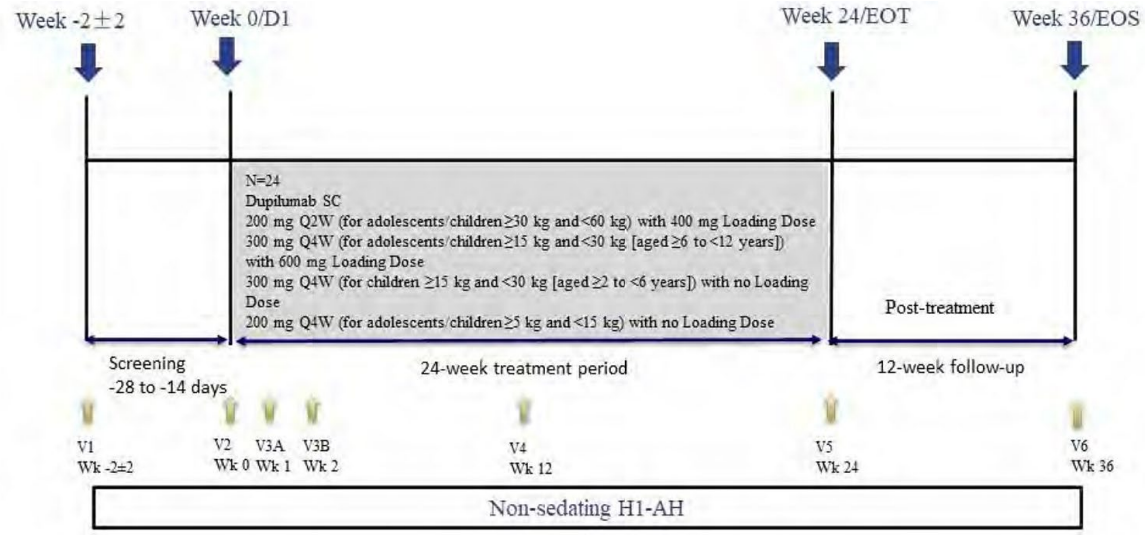
PKM16982

Study PKM16982 was a Phase 3, multicenter, single-arm, 24-week treatment PK/safety study in male and female participants ≥2 years to <12 years of age with a physician diagnosis of CSU for at least 3 months despite regular use of H1-antihistamines during this time period. Participants with underlying etiology for chronic urticaria other than CSU were excluded.

Methods

The study consisted of 3 periods with a total duration of up to 40 weeks for each participant: screening period (2 to 4 weeks), treatment period (24 weeks), and post-treatment follow-up period (12 weeks).

Design of Study PKM16982



Abbreviations: D = day; EOT = End of Treatment; EOS = End of Study; H1-AH = H1-Antihistamines; N = number of participants; q2w = every 2 weeks; q4w = every 4 weeks; SC = subcutaneous; V = visit; Wk = week.

Study participants

Key inclusion criteria were:

- Participant must be ≥2 years to <12 years of age, at the time of signing the informed consent.
- Participants who have history of a diagnosis of CSU prior to screening (V1) or symptoms consistent with a diagnosis of CSU for at least 3 months in the Investigator's opinion.
- Participants with CSU (characterized by recurrent itchy wheals with or without angioedema for >6 weeks) who remain symptomatic at the time of screening despite regular H1-antihistamine treatment.
- Body weight within ≥5 kg to <60 kg.

Key exclusion criteria were:

- Underlying etiology for chronic urticarias other than CSU including but not limited to forms of inducible urticaria or diseases with possible symptoms of urticaria or angioedema
- Presence of skin morbidities other than CSU that may interfere with the assessment of the study outcomes.
- Participants with a concurrent diagnosis of chronic inducible cold urticaria.
- Participants with active AD.
- Participant who has taken biologic therapy (disease modifiers)/systemic immunosuppressant/immunomodulator within 4 weeks before the screening visit (V1) or 5 half-lives, whichever is longer.
- Prior use of omalizumab.
- Participation in prior dupilumab clinical study or have been treated with commercially available dupilumab.
- Use of any prohibited medications and procedures during screening period or planned use during screening or study treatment period.

Treatments

This was an uncontrolled single-arm trial.

Dupilumab SC regimens based on the participant's weight and age were as follows:

≥5 kg and <15 kg:	200 mg q4w with an initial dose of 200 mg (ie. no LD)
≥15 kg and <30 kg (aged ≥2 to <6 years old)	300 mg q4w with an initial dose of 300 mg (ie, no LD)
≥15 kg and <30 kg (aged ≥6 to <12 years old)	300 mg q4w with an initial 600 mg LD[*1]
≥30 kg and <60 kg:	200 mg q2w with an initial 400 mg LD[*2]

[*1]: 2 × 300 mg injections (300 on Day 1, followed by 300 mg on Day 15); [*2]: 2 × 200 mg injection

Background Medication

It was recommended that participants continue their established standard of care background therapy with a long-acting non-sedating H1-antihistamines (for Japan, up to 2-fold the licensed dose). For Study PKM16982, any dosing schedule of H1-antihistamines was permissible (daily, any number of days per week) and participants did not need to be on a stable dose of H1 antihistamines prior to enrolment.

Rescue Medication

Participants were allowed to increase the dose of their background H1-antihistamine as rescue therapy as long as they do not exceed 4-fold the licensed dose for CSU during the treatment and follow-up periods. If symptoms are still uncontrolled after increase of H1-antihistamine to the maximum allowed dose, or if the participant is already on the 4-fold H1-antihistamine, participants could switch to another H1-antihistamine up to 4-fold the licensed dose for CSU or alternatively, a short course of OCS was allowed during the treatment and follow-up periods.

Objectives

Primary Objective

- The primary objective of the PKM16982 was to characterize the serum concentration of dupilumab over time in children with CSU aged ≥2 to 12 years who remain symptomatic despite the use of H1-antihistamine.

Secondary objectives:

- To assess the safety and immunogenicity of dupilumab.
- To evaluate the improvement in HRQoL in participants with CSU receiving dupilumab who remain symptomatic despite the use of H1-antihistamine.
- To assess the impact of dupilumab on urticaria activity, itch and hives severity scores in participants with CSU who remain symptomatic despite the use of H1-antihistamine.

Outcomes/endpoints

Primary endpoint:

- Concentration of dupilumab in serum over time including Ctrough at Week 12 and Week 24.

Secondary endpoints:

- Safety and tolerability assessments: Incidence of TEAEs or SAEs.
- Incidence of ADA to dupilumab over time.
- Change from baseline in C-DLQI in children from 4 years to less than 12 years of age at Week 24.
- Change from baseline in IDQOL in children from 2 years to less than 4 years of age at Week 24.
- Change from baseline in the modified UAS7a at Week 24.
- Change from baseline in the ISS7 at Week 24.
- Change from baseline in the HSS7 at Week 24.

A modified UAS7 was utilized to account for the smaller body surface area in children, such that for wheals, 0 = symptom is absent; 1 = mild:(1 to <10 wheals/24 h); 2 = moderate: (10 to 30 wheals/24h); and 3 = intense: (>30 wheals/24 h or large confluent areas of wheals). The measures of pruritus remained unchanged from the adult scale.

Sample size

The number of participants was based on practical considerations and clinical judgment since this study was a single arm study with the primary endpoint being based on a PK parameter. The study was not powered for hypothesis testing of efficacy endpoints. A minimum of 8 participants per weight group (≥5 kg to <30 kg and ≥30 kg to <60 kg) and a total of 24 participants were considered adequate by the applicant to provide precision in PK parameters for participants aged ≥2 years to <12 years.

Randomisation

Not applicable as this was a single-arm study.

Blinding (masking)

Not applicable.

Statistical methods

Primary Endpoint:

Serum concentrations of dupilumab including Ctrough at Week 12 and Week 24 were to be summarized in the PK population using arithmetic and geometric means, SD, SEM, CV, minimum, median, and maximum per sampling time. Please also refer to Section 2.3.2. .

Secondary Endpoints:

Efficacy was evaluated as part of the secondary endpoints. The efficacy analysis was conducted on the ITT population. Continuous efficacy secondary endpoints were summarized using descriptive statistics (number of observations available, mean and the corresponding 95% CI, SD, median, minimum, and maximum).

Results

Participant flow

A total of 15 participants were enrolled and treated with dupilumab comprising the ITT population. Of the 15 participants enrolled, 14 (93.3%) completed the study period and 1 (6.7%) participant in the 300 mg q4w did not complete the 24-week study treatment period due to "withdrawal by the subject".

Recruitment

First participant enrolled:	25 August 2022
Last participant last visit:	03 February 2025
The primary analysis data cut-off:	28 February 2025

Conduct of the study

Protocol amendments

The original protocol dated 30 March 2022 was modified once with amendment 01 dated 31 May 2023.

The purpose of this amendment was to remove the inclusion of patients with chronic inducible cold urticaria (CICU) following the results of the phase 3 study EFC16720, which evaluated the efficacy and safety of dupilumab in adult patients with CICU who remained symptomatic despite the use of H1-antihistamine treatment. This study did not meet the required efficacy endpoints to continue this program, including the development in the paediatric CICU population. In addition, the inclusion criteria and the PK sampling schedule to increase flexibility were modified.

Protocol deviations

Major protocol deviations were reported in 8 (53.3%) participants. The most frequently reported protocol deviations (≥2 participants) were as follows:

- Deviations related to "Planned sample (PK) not performed" were reported in 4 (26.7%) participants: 3 participants from the dupilumab 300 mg q4w with no LD and 1 participant from the dupilumab 200 mg q2w with a 400 mg LD.

- Deviation related to informed consent process was reported as "Study informed consent/assent form not obtained for the substudy/exploratory analyses/DNA banking but substudy/exploratory analysis/DNA banking performed" in 3 (20.0%) participants: 2 participants from the dupilumab 300 mg q4w with no LD and 1 participant from the dupilumab 200 mg q2w with a 400 mg LD.
- Deviation related to inclusion/exclusion criteria was reported as "Participant who has taken biologic therapy (disease modifiers)/systemic immunosuppressant/immunomodulator within 4 weeks before the screening visit (v1) or 5 half-lives, whichever is longer" in 2 (13.3%) participants from the dupilumab 200 mg q2w with a 400 mg LD.
- In 2 (13.3%) participants from the dupilumab 200 mg q2w with a 400 mg LD, deviations related to "Protocol prohibited therapy/medication/vaccine/administered" were reported.

Baseline data

Demographics

Table 14. Demographics and participant characteristics at baseline - Safety population - Study PKM16982

	200 mg Q4W (N=1)	300 mg Q4W (N=4)	300 mg Q4W, 600 mg LD (N=2)	200 mg Q2W, 400 mg LD (N=8)	All (N=15)
Age (years)					
Number	1	4	2	8	15
Mean (SD)	6.0	3.0 (0.8)	7.0 (1.4)	8.6 (2.0)	6.7 (2.9)
Median		3.0	7.0	8.5	6.0
Min ; Max	6 ; 6	2 ; 4	6 ; 8	6 ; 11	2 ; 11
Age group (years) [n (%)]					
Number	1	4	2	8	15
≥2 to <6 years	0	4 (100)	0	0	4 (26.7)
≥6 to <12 years	1 (100)	0	2 (100)	8 (100)	11 (73.3)
Sex [n (%)]					
Number	1	4	2	8	15
Male	0	2 (50.0)	0	2 (25.0)	4 (26.7)
Female	1 (100)	2 (50.0)	2 (100)	6 (75.0)	11 (73.3)
Ethnic Origin [n (%)]					
Number	1	4	2	8	15
White	0	4 (100)	1 (50.0)	4 (50.0)	9 (60.0)
Black or African American	0	0	0	1 (12.5)	1 (6.7)
Asian	1 (100)	0	1 (50.0)	2 (25.0)	4 (26.7)
Asian Indian	0	0	0	1 (12.5)	1 (6.7)
Japanese	1 (100)	0	1 (50.0)	1 (12.5)	3 (20.0)
Unknown	0	0	0	1 (12.5)	1 (6.7)
Hispanic Ethnicity [n (%)]					
Number	1	4	2	8	15
Not Hispanic or Latino	1 (100)	4 (100)	2 (100)	7 (87.5)	14 (93.3)
Hispanic or Latino	0	0	0	1 (12.5)	1 (6.7)

	200 mg Q4W (N=1)	300 mg Q4W (N=4)	300 mg Q4W, 600 mg LD (N=2)	200 mg Q2W, 400 mg LD (N=8)	All (N=15)
Baseline Weight (kg)					
Number	1	4	2	8	15
Mean (SD)	14.50	18.38 (2.33)	25.65 (0.78)	36.85 (5.00)	28.94 (9.89)
Median		17.90	25.65	37.80	30.80
Min ; Max	14.5 ; 14.5	16.2 ; 21.5	25.1 ; 26.2	30.8 ; 44.7	14.5 ; 44.7
Baseline Weight by category (kg) [n (%)]					
Number	1	4	2	8	15
<15 kg	1 (100)	0	0	0	1 (6.7)
≥15 to <30 kg	0	4 (100)	2 (100)	0	6 (40.0)
≥30 kg	0	0	0	8 (100)	8 (53.3)

Abbreviations: LD = loading dose; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = standard deviation; N = number of participants in each intervention group or overall population.

Baseline disease characteristics

Table 15. Baseline disease characteristics and baseline H1-AH medications - ITT population - Study PKM16982

	200 mg Q4W (N=1)	300 mg Q4W (N=4)	300 mg Q4W, 600 mg LD (N=2)	200 mg Q2W, 400 mg LD (N=8)	All (N=15)
ISS7					
Number	1	3	2	8	14
Mean (SD)	7.0	8.9 (7.8)	12.1 (4.4)	10.2 (5.4)	10.0 (5.3)
Median		7.0	12.1	11.5	9.0
Q1 ; Q3	7.0 ; 7.0	2.3 ; 17.5	9.0 ; 15.2	6.4 ; 14.5	7.0 ; 15.0
Min ; Max	7 ; 7	2 ; 18	9 ; 15	1 ; 16	1 ; 18
HSS7					
Number	1	3	2	8	14
Mean (SD)	7.0	9.4 (7.1)	9.2 (10.1)	9.9 (5.1)	9.5 (5.5)
Median		13.0	9.2	10.7	10.7
Q1 ; Q3	7.0 ; 7.0	1.2 ; 14.0	2.0 ; 16.3	7.4 ; 13.5	5.8 ; 14.0
Min ; Max	7 ; 7	1 ; 14	2 ; 16	0 ; 16	0 ; 16
mUAS7					
Number	1	3	2	8	14
Mean (SD)	14.0	18.3 (14.1)	21.3 (14.5)	20.1 (10.4)	19.4 (10.4)
Median		20.0	21.3	22.5	19.0
Q1 ; Q3	14.0 ; 14.0	3.5 ; 31.5	11.0 ; 31.5	14.0 ; 27.5	11.0 ; 28.0
Min ; Max	14 ; 14	4 ; 32	11 ; 32	1 ; 32	1 ; 32
C-DLQI score					
Number	1	1	2	7	11
Mean (SD)	6.0	7.0	12.5 (4.9)	9.4 (4.6)	9.5 (4.3)
Median			12.5	9.0	9.0
Q1 ; Q3	6.0 ; 6.0	7.0 ; 7.0	9.0 ; 16.0	5.0 ; 13.0	6.0 ; 13.0
Min ; Max	6 ; 6	7 ; 7	9 ; 16	4 ; 17	4 ; 17
IDQOL score					
Number	0	2	0	0	2
Mean (SD)		4.0 (2.8)			4.0 (2.8)
Median		4.0			4.0
Q1 ; Q3		2.0 ; 6.0			2.0 ; 6.0
Min ; Max		2 ; 6			2 ; 6
Baseline antihistamines [n(%)]					
Any antihistamine	1 (100)	4 (100)	2 (100)	8 (100)	15 (100)
BILASTINE	0	0	1 (50.0)	1 (12.5)	2 (13.3)

	200 mg Q4W (N=1)	300 mg Q4W (N=4)	300 mg Q4W, 600 mg LD (N=2)	200 mg Q2W, 400 mg LD (N=8)	All (N=15)
CETIRIZINE HYDROCHLORIDE	0	3 (75.0)	0	4 (50.0)	7 (46.7)
FEXOFENADINE	0	0	0	1 (12.5)	1 (6.7)
FEXOFENADINE HYDROCHLORIDE	0	0	1 (50.0)	0	1 (6.7)
LORATADINE	1 (100)	2 (50.0)	0	2 (25.0)	5 (33.3)
RUPATADINE FUMARATE	0	0	0	1 (12.5)	1 (6.7)

Numbers analysed

All 15 participants were included in the ITT, PK, and safety populations. The ADA population comprised 14 participants.

Outcomes and estimation

The efficacy of dupilumab in paediatric participants with CSU was investigated as secondary objectives. All efficacy endpoints were analyzed descriptively.

Children's Dermatology Life Quality Index (participants aged 4 to <12 years)

C-DLQI data were obtained for a total of 11 participants aged 4 to <12 years. Baseline C-DLQI scores ranged from 4 to 17 (scale range: 0-30 for children ≥4 to <16 years old with a higher score indicative of a poorer quality-of-life), with an overall mean (SD) C-DLQI of 9.5 (4.3).

Table 16. Descriptive statistics of C-DLQI total scores - Participants from 4 years to less than 12 years of age - ITT population - Study PKM16982

	200 mg Q4W (N=1)	300 mg Q4W (N=4)	300 mg Q4W, 600 mg LD (N=2)	200 mg Q2W, 400 mg LD (N=8)	All (N=15)
Baseline					
Number	1	1	2	7	11
Mean (SD)	6.0	7.0	12.5 (4.9)	9.4 (4.6)	9.5 (4.3)
Median			12.5	9.0	9.0
Q1 ; Q3			9.0 ; 16.0	5.0 ; 13.0	6.0 ; 13.0
Min ; Max	6 ; 6	7 ; 7	9 ; 16	4 ; 17	4 ; 17
Week 24					
Number	1	1	2	8	12
Mean (SD)	3.0	1.0	2.0 (1.4)	2.0 (1.5)	2.0 (1.3)
Median			2.0	2.0	2.0
Q1 ; Q3			1.0 ; 3.0	1.0 ; 2.5	1.0 ; 3.0
Min ; Max	3 ; 3	1 ; 1	1 ; 3	0 ; 5	0 ; 5
Change from baseline					
Number	1	1	2	7	11
Mean (SD)	-3.0	-6.0	-10.5 (3.5)	-7.3 (4.3)	-7.4 (4.1)
Median			-10.5	-6.0	-6.0

	200 mg Q4W (N=1)	300 mg Q4W (N=4)	300 mg Q4W, 600 mg LD (N=2)	200 mg Q2W, 400 mg LD (N=8)	All (N=15)
Q1 ; Q3			-13.0 ; -8.0	-11.0 ; -5.0	-11.0 ; -5.0
Min ; Max	-3 ; -3	-6 ; -6	-13 ; -8	-15 ; -2	-15 ; -2

Abbreviations: LD = loading dose; Q2W = every 2 weeks; Q4W = every 4 weeks; C-DLQI = children's dermatology life quality index; SD = standard deviation; Q1 = first quartile; Q3 = third quartile;
N = number of participants in each intervention group or overall population.
"Number" corresponds to the count of participants with available data.
Note: Baseline is considered as the closest assessment to the first investigational medicinal product (IMP) administration on or prior to Day 1 but no later than Day 4.

Infant's Dermatitis Quality of Life Index (participants aged ≥2 to <4 years)

IDQOL data were obtained in the dupilumab 300 mg q4w without a LD group for a total of 2 participants aged ≥2 to <4 years at baseline and 1 participant at Week 24, due to study treatment discontinuation in 1 participant prior to Week 24.

Table 17. Descriptive statistics of IDQOL total scores and global dermatitis severity - Participants from 2 years to less than 4 years of age - ITT population

	200 mg Q4W (N=1)	300 mg Q4W (N=4)	300 mg Q4W, 600 mg LD (N=2)	200 mg Q2W, 400 mg LD (N=8)	All (N=15)
Baseline					
Number	0	2	0	0	2
Mean (SD)		1.0 (1.4)			1.0 (1.4)
Median		1.0			1.0
Q1 ; Q3		0.0 ; 2.0			0.0 ; 2.0
Min ; Max		0 ; 2			0 ; 2
Week 24					
Number	0	1	0	0	1
Mean (SD)		1.0			1.0

Abbreviations: LD = loading dose; Q2W = every 2 weeks; Q4W = every 4 weeks; C-DLQI = children's dermatology life quality index; SD = standard deviation; Q1 = first quartile; Q3 = third quartile;
N = number of participants in each intervention group or overall population.
"Number" corresponds to the count of participants with available data.
Note: Baseline is considered as the closest assessment to the first investigational medicinal product (IMP) administration on or prior to Day 1 but no later than Day 4.

Modified Urticaria Activity Score over 7 days

There were no restrictions in mUAS7 score at the time of screening for Study PKM16982. Baseline mUAS7 ranged from 1 to 32, with an overall mean (SD) mUAS7 of 19.4 (10.4).

Table 18. Descriptive statistics of mUAS7 at baseline and Week 24 - ITT population - Study PKM16982

	200 mg Q4W (N=1)	300 mg Q4W (N=4)	300 mg Q4W, 600 mg LD (N=2)	200 mg Q2W, 400 mg LD (N=8)	All (N=15)
Baseline					
Number	1	3	2	8	14

Mean (SD)	14.0	18.3 (14.1)	21.3 (14.5)	20.1 (10.4)	19.4 (10.4)
Median		20.0	21.3	22.5	19.0
Q1 ; Q3		3.5 ; 31.5	11.0 ; 31.5	14.0 ; 27.5	11.0 ; 28.0
Min ; Max	14 ; 14	4 ; 32	11 ; 32	1 ; 32	1 ; 32
Week 24					
Number	1	3	2	5	11
Mean (SD)	6.0	2.9 (5.1)	18.5 (16.3)	7.0 (7.1)	7.9 (9.1)
Median		0.0	18.5	8.0	7.0
Q1 ; Q3		0.0 ; 8.8	7.0 ; 30.0	0.0 ; 10.0	0.0 ; 10.0
Min ; Max	6 ; 6	0 ; 9	7 ; 30	0 ; 17	0 ; 30
Change from baseline					
Number	1	2	2	5	10
Mean (SD)	-8.0	-21.4 (1.9)	-2.8 (1.8)	-7.8 (6.6)	-9.5 (8.0)
Median		-21.4	-2.8	-8.0	-8.0
Q1 ; Q3		-22.8 ; -20.0	-4.0 ; -1.5	-10.2 ; -2.5	-17.5 ; -2.5
Min ; Max	-8 ; -8	-23 ; -20	-4 ; -2	-18 ; -1	-23 ; -1

Abbreviations: LD = loading dose; Q2W = every 2 weeks; Q4W = every 4 weeks; mUAS7 = (modified) urticaria activity score over 7 days; SD = standard deviation; Q1 = first quartile; Q3 = third quartile;
N = number of participants in each intervention group or overall population.
"Number" corresponds to the count of participants with available data.
Note: Baseline is the sum of the 7 daily measurements obtained within the 7 days prior to first investigational medicinal product (IMP) administration.

Overall, the mean (SD) numerical improvement was 9.5 (8.0). Of the 15 included children, 9 presented with moderate-to-severe CSU (mUAS7 ≥16) at baseline (range 18 to 32). At Week 24, data were available for 6 participants with the mean (SD) change from baseline of -13.3 (8.1) (range -23 to -2).

Itch Severity Score over 7 days

Baseline ISS7 ranged from 1 to 18, with an overall mean (SD) ISS7 of 10.0 (5.3). A numerical improvement (reduction) in urticaria activity as measured by ISS7 was observed at Week 24 in all participants regardless of dosing regimen, with a mean change from baseline of 5.0 in the dupilumab 200 mg q4w (N=1), -9.6 (3.7) in the dupilumab 300 mg q4w (N=2), 1.6 (0.6) in the dupilumab 300 mg q4w, 600 mg LD (N=2), and -3.4 (3.2) in the dupilumab 200 mg q2w, 400 mg LD (N=5). Overall, the mean (SD) numerical improvement was -4.4 (3.8).

Hive Severity Score over 7 days

Baseline HSS7 ranged from 0 to 16, with an overall mean (SD) HSS7 of 9.5 (5.5). Overall, there was a decrease in hives severity from baseline as measured by mean HSS7 at Week 24 regardless of dosing regimen, with a mean (SD) change from baseline of -3.0 in the dupilumab 200 mg q4w (N=1), -11.8 (1.8) in the dupilumab 300 mg q4w (N=2), -1.2 (1.2) in the dupilumab 300 mg q4w, 600 mg LD (N=2), and -4.4 (3.6) in the dupilumab 200 mg q2w, 400 mg LD (N=5). Overall, the mean (SD) numerical improvement in mean (SD) HSS7 was 5.1 (4.5).

EFC16461 Study A and C

EFC16461 Study A and Study C were 2 similar randomized, double-blind, placebo-controlled, parallel group studies of dupilumab in adults, adolescents aged 12 to <18 years, and children aged 6 to <12 years with CSU inadequately controlled with H1-antihistamine and naïve to omalizumab. For study

eligibility, participants had to present with itch and hives for more than 6 consecutive weeks at any time prior to screening, despite the use of H1-antihistamines during this time period. Participants had to have UAS7 ≥16 and ISS7 ≥8 with no missing UAS7 and ISS7 recording in the electronic diary during the 7 days before randomization.

Efficacy data for adults and adolescents (≥12 years) obtained from these studies have been evaluated as part of the variation procedure EMA/VR/0000257461. Please refer to the respective report for a detailed overview on the study design and efficacy results for this age group.

In this report, efficacy data for patients aged 6 to <12 years from studies A and C will be presented.

Methods

The study consisted of 3 periods:

- Screening period (2 to 4 weeks)
- IMP treatment period (24 weeks ± 3 days)
- Post IMP treatment period (12 weeks ± 3 days)

Study participants

Key inclusion criteria were:

- Participants ≥6 to 80 years of age at the time of signing the informed consent
- Diagnosis of CSU >6 months prior to screening visit
- Presence of itch and hives for >6 consecutive weeks at any time prior to screening visit despite the use of H1-antihistamine during that time period.
- Participants using a study defined H1-antihistamine for CSU treatment and who were on a stable H1-antihistamine dose* for at least 3 consecutive days prior to the screening visit
- During the 7 days before randomization: UAS7 ≥16 and ISS7 ≥8, with no missing electronic diary (ediary) (UAS7 and ISS7).
- Participants who were omalizumab naïve.

Key exclusion criteria were:

- Body weight less than 30 kg in adults and adolescents and 15 kg in children aged ≥6 to <12 years
- Clearly defined underlying etiology for chronic urticarias other than CSU (main manifestation being physical urticaria), such as inducible urticaria and diseases with possible symptoms of urticaria or angioedema.
- Presence of skin morbidities other than CSU that may interfere with the assessment of the study outcomes.
- Patients with active AD.
- Treatment with biologics as follows: Any cell-depleting agents including but not limited to rituximab within 6 months before the screening visit; Omalizumab within 4 months before the screening visit; other monoclonal antibodies (which are biological response modifiers): within 5 half-lives (if known) or 16 weeks before the screening visit (Visit 1), whichever is longer.

Treatments

Dupilumab

Dupilumab 300 mg q2w*[1] (adults and those adolescents ≥60 kg)

Dupilumab 200 mg q2w*[2] (adolescents <60 kg)

Dupilumab 300 mg q4w*[1] (children ≥6 to <12 years of age <30 kg and ≥15 kg)

*[1] initial loading dose of 600 mg, *[2] initial loading dose of 400 mg

Placebo

Placebo administered as 1 SC injection of placebo matching dupilumab 300 mg or 200 mg

Background Medication

Participants were expected to continue their established standard of care background therapy with long-acting non-sedating H1-antihistamines, at up to 4-fold the recommended dose (up to 2-fold for participants in Japan). Participants were expected to continue to take the same daily dose throughout the study unless they experienced a flare for which rescue therapy might be initiated.

Rescue Medication

All participants on 1- to 3-fold the approved H1-antihistamine dose (maintenance dose used at screening) were allowed to take additional doses of their H1-antihistamine medications as rescue therapy as long as they did not exceed 4-fold the recommended dose (up to 2-fold for participants in Japan) during the study. If symptoms were still uncontrolled after receiving the maximum allowed dose (ie, 4-fold the recommended dose) of H1-antihistamine, or participants already using the maximum allowed H1-antihistamine dose could take a short course of OCS as rescue therapy during the treatment and follow-up periods.

Outcomes/endpoints

Primary objectives/endpoints:

- To demonstrate the efficacy of dupilumab in study participants with CSU who remain symptomatic despite the use of H1-antihistamines in omalizumab naïve patients

The primary objective of both studies was to evaluate the efficacy of dupilumab compared with placebo in improving urticaria activity as measured by UAS7 in participants with CSU.

Secondary endpoints:

Secondary endpoints further evaluated improvements in itch and hives symptoms as measured by ISS7 and HSS7 and quality of life using CDLQI in patients ≥6 to <12 years of age.

Results

Participant flow

A total of 5 participants aged ≥6 to <12 years old were enrolled in EFC16461 Study A and Study C. In Study A, 1 male (8 years; 32.5 kg) and 1 female participant (10 years; 55.7 kg) received dupilumab 200 mg q2w (with a LD of 400 mg). Both discontinued treatment permanently (after Week 10 and Week 4, respectively), with lack of efficacy as the reported reason for discontinuation. In Study C, 1 male participant (11 years; 45.3 kg) received dupilumab 200 mg q2w (with a LD of 400 mg) and 2 female participants (11 years; 37.8 kg / 8 years; 32.7 kg) received placebo; all until Week 24.

Recruitment (adults, adolescents, children)

	Study (A)	Study (C)
First participant enrolled:	06 February 2020	02 August 2022
Last participant last visit:	26 August 2021	01 August 2024
The primary analysis data cut-off:	05 October 2021	20 August 2024

Conduct of the study

Please also refer to the EPAR of EMA/VR/0000257461 on the EMA website.

Baseline data

Demographics

Study A and Study C, enrolled 5 participants aged ≥6 to <12 years old. In particular, study A included one male participant 8 years old (32.5 kg) and one female participant 10 years old (55.7 kg). Both were treated with dupilumab. Study C enrolled two female participants 11 years old (37.8 kg) and 8 years old (32.7 kg) (treated with dupilumab) and 1 male participant 11 years old (45.3 kg) treated with placebo. At study entry, all participants received background H1-antihistamines for moderate-to-severe CSU.

Outcomes and estimation

Children's Dermatology Life Quality Index

Table 19. Listing of C-DLQI data in children at baseline, Week 12, and Week 24 - ITT population - EFC16461 Study A and Study C

Participant	Intervention group	Age (yrs) /Sex[a] /Weight (kg)	Time-point	C-DLQI
STUDY A				
	Dupilumab 200 mg q2w	8/M/32.5	Baseline	16
			Week 12	12
	Dupilumab 200 mg q2w	10/F/55.7	Baseline	6
			Week 6[b,c]	-
STUDY C				

Participant	Intervention group	Age (yrs) /Sex[a] /Weight (kg)	Time-point	C-DLQI
	Placebo	11/F/37.8	Baseline	9
			Week 12	17
			Week 24	14
	Placebo	8/F/32.7	Baseline	6
			Week 12	4
			Week 24	0
	Dupilumab 200 mg q2w	11/M/45.3	Baseline	11
			Week 12	0
			Week 24	1

Abbreviations: C-DLQI = Children's Dermatology Quality of Life (0-30); DLQI = Dermatology Quality of Life.
a M = Male, F = Female.
b Participant incorrectly completed DLQI instead of C-DLQI.
c The participant stopped IMP after Week 4 and received rescue therapy during the week prior to the end of study visit (Week 7).

Urticaria Activity Score over 7 days

In EFC16461 Study A and C, an UAS7 of at least 16 was required for enrolment. Treatment with dupilumab resulted in a numerical improvement in UAS7. In 1 participant that received dupilumab in Study C, a complete response (UAS7 = 0) was achieved at Week 12, while the other 2 participants in Study A who were treated with dupilumab discontinued due to lack of efficacy.

Table 20. Listing of UAS7 data in children at baseline, Week 12, and Week 24 - ITT population - EFC16461 Study A and C

Participant	Intervention group	Age (yrs) /Sex[a] /Weight (kg)	Time-point	UAS7
STUDY A				
	Dupilumab 200 mg q2w	8/M/32.5	Baseline	16
			Week 12	14
	Dupilumab 200 mg q2w	10/F/55.7	Baseline	31
			Week 6[b]	28
STUDY C				
	Placebo	11/F/37.8	Baseline	42
			Week 24	42
	Placebo	8/F/32.7	Baseline	30
			Week 12	14
			Week 24	0
	Dupilumab 200 mg q2w	11/M/45.3	Baseline	35
			Week 12	0
			Week 24	2

Abbreviations: UAS7 = urticaria activity score over 7 days (0-42).
a M = Male, F = Female.

b The participant stopped IMP after Week 4 and received rescue therapy during the week prior to the end of study visit (Week 7).

Itch Severity Score over 7 days

In the EFC16461 Study A and Study C, treatment with dupilumab resulted in a numerical improvement in ISS7 in 2 out of 3 participants.

Hive Severity Score over 7 days

In the EFC16461 Study A and Study C, treatment with dupilumab resulted in a numerical improvement in HSS7 in 2 out of 3 participants.

2.4.3. Discussion on clinical efficacy

This variation concerns the extension of indication for the treatment of children aged ≥2 to <12 years old with moderate-to-severe CSU.

The following indication is discussed: "Dupixent is indicated for the treatment of moderate-to-severe chronic spontaneous urticaria (CSU) in adults, adolescents, and children (2 years and above) with inadequate response to H1 antihistamines and who are naive to anti-IgE therapy for CSU".

The claims for efficacy are based on the extrapolation from adult and adolescent CSU patients ≥12 years with the same line of treatment that that has been recently approved (EMA/VR/0000257461). Supportive clinical efficacy data are derived from paediatric CSU patients included in the phase 3 PK/safety study **PKM16982** and from the two phase 3 studies **EFC16461 Study A** and **Study C**. The latter studies that primarily included adult and adolescent patients have been extensively reviewed in EMA/VR/0000257461.

Depending on the participant's weight that was planned to be in the range between 5 and 60 kg, dupilumab was given at 200 mg q4w, 300 mg q4w, or 200 mg q2w. Dose regimens for participants above 15 kg with an age ≥6 years included a loading dose. These dosing regimens are also in part already used for the treatment of children with atopic dermatitis, however differences exist regarding the dose for children with body weight ≥30 kg and <60 kg that uses a loading dose (see PK/PD assessment in 9.2 for further details).

Design and conduct of clinical studies

PKM16982

Study design

Study PKM16982 was a single-arm, PK/safety study in paediatric CSU patients ≥2 years to <12 years of age with 24-week treatment and 12-week follow-up period. Participants had to have a diagnosis of CSU for at least 3 months despite regular use of H1-antihistamines during this time period. Any dosing schedule of H1-antihistamines was permissible and participants did not need to be on a stable dose of H1-antihistamines prior to enrolment. In addition, a certain level of disease severity (as measured by mUAS7 score) was not required for enrolment. This renders the study population less severe as the enrolled adult/adolescent population. Participants could increase H1-antihistamines up-to 4x the recommended dose or take a short course of oral corticosteroids as rescue medication.

The primary objective of the PKM16982 was to characterize the serum concentration of dupilumab over time in children with CSU while efficacy outcomes were evaluated at Week 24 as part of the secondary endpoints including validated quality of life measures (IDQOL, C-DLQI) and measures to evaluate CSU symptoms (mUAS7, ISS7, HSS7). A modified version of the UAS (mUAS) that uses lower wheal count

thresholds in the HSS component was used to account for the smaller body surface area in children. This modified score was not validated, but is considered acceptable given the small paediatric population enrolled and the only descriptive data obtained from the study.

With the primary objective on PK, the study was not powered for hypothesis testing of efficacy endpoints. Based on practical reasons, a minimum of 8 participants per weight group (≥5 kg to <30 kg and ≥30 kg to <60 kg) and a total of 24 participants were initially planned. Due to recruitment challenges, the enrolment was stopped at a total of 15 participants with 7 and 8 participants included in the two weight groups, respectively. As regards the efficacy evaluation, this lower number of participants is not optimal but is considered acceptable, as data obtained only provide supportive descriptive data and the efficacy claim will mainly rely on an extrapolation approach.

Study conduct

The study was conducted between August 2022 and February 2025. Of the 15 participants enrolled, 14 completed the study period while 1 participant discontinued treatment and withdrew from study at day 85.

Baseline data

The lowest age range (2-6 years) and the lowest weight category (>15kg) was only covered by one participant in each group. All other 13 participants had an age of ≥6 years with the oldest participant being 11 years old.

EFC16461 Study A & C

Study design

EFC16461 Study A and Study C were placebo-controlled, phase 3 efficacy and safety, mainly conducted in adults and adolescents with CSU inadequately controlled with H1-antihistamine and naïve to omalizumab which also enrolled a small cohort of children aged 6 to <12 years (n=5). The study included 24-week treatment and 12-week follow-up period. Participants had to present with itch and hives for more than 6 consecutive weeks, despite the use of H1-antihistamines during this period. The study included participants with moderate-to-severe disease as defined by an UAS7 ≥16.

As for study PKM16982, the efficacy assessment in EFC16461 Study A & C included quality of life measures (ie. C-DLQI) as well as the unmodified UAS7, ISS7, and HSS7 scores to evaluate symptom severity.

Study conduct

Study A and C were sequentially initiated and conducted between February 2020 and August 2025. A total of 5 participants aged ≥6 to <12 years old were enrolled (A: n=2; C: n=3). In Study A, both enrolled participants received dupilumab but discontinued treatment due to lack of efficacy. In Study C, one participant received dupilumab and two participants received placebo without discontinuation until Week 24.

Assessment of paediatric data on clinical efficacy

In the three studies combined (PKM16982, and EFC16461 Study A & C), a total of 20 children with an age ≥2 to <12 years was included. Given this low number of participants, only descriptive analyses can be made.

In study PKM16982, change from baseline values for C-DLQI were available for 11 participants in total. While descriptive and uncontrolled in nature, the changes in C-DLQI at Week 24 tend to show improvements in the different dose groups evaluated, while improvements were the most pronounced

in the higher body weight groups (300mg Q4W and 200mg Q2W). The mean (SD) numerical improvement for all 11 participants was -7.4 (4.1). C-DLQI scores were also available from 3 participants treated with dupilumab in the studies EFC16461, however two of them discontinued treatment due to lack of efficacy.

IDQOL for children below 4 years were available at Week 24 for only one participant and suggest the disease impact on QoL was rather low for this particular participant and also remained unchanged after 24 weeks.

In study PKM16982, a modified UAS7 score was used and participants were not required to present with a certain disease severity at study entry. Consequently, the baseline UAS7 scores were overall lower, as compared to the adult population with a min/max range of 1 to 32 (mean: 19.4). Some participants were enrolled with a rather mild disease severity which limits the evaluation of changes in symptom improvements and the ability to compare the data from children with those obtained in adults. Moreover, UAS7 scores are missing at baseline or at Week 24 for a total of 5/15 of enrolled patients. Thus, change from baseline values are only available for 10 participants making the data even more limited. Missing data were mainly due to poor compliance with required eDiary assessment for mUAS7 scoring. Overall, the mean (SD) numerical improvement was -9.5 (8.0). While the symptom improvements covered a wide span (min/max: -23 to -1), the data at least suggest that there was no worsening of symptoms under treatment with dupilumab. Data from three additional dupilumab-treated children were obtained from studies EFC16461 Study A & C which may suggest a similar trend but which are also very limited as Week 24 data were only available for one participant as the other two discontinued treatment due to lack of efficacy. The limited paediatric data from EFC16461 studies are thus not considered supportive.

When compared to the adult/adolescent population (EPAR EMA/VR/0000257461 available on the EMA website), the mean change from baseline in UAS7 observed study PKM16982 lies in the range of the observed UAS7 response of the control arm which raises uncertainty as regards the meaningfulness of improvements observed in children. As PKM16982 study data are uncontrolled, the magnitude of a placebo response in the children population remains unknown and it remains unclear whether this would be similar to the adult population. Also considering the differences in the study population (less severe), a clear comparison between in UAS7 children and adults is limited. For participants with mUAS7 ≥16 at baseline which would be in line with the adult studies, a higher mean (SD) change from baseline (-13.3 (8.1); range -23 to -2) was observed which at least points towards a similar response in this subgroup.

Overall, the clinical data from study PKM16982 only provide some limited level of support showing similar trends in improvements in symptoms and quality-of-life while uncertainties (uncontrolled study, limited patient number, missing data, less severe study population, modified UAS7 used) need to be considered. Given these inherent limitations, the efficacy claim relies on an extrapolation approach (as also assessed in section 2.4.4. .).

Extrapolation from adults/adolescents to children

The applicant's reasoning for the proposed efficacy extrapolation assumes a similar disease pathology between children and adolescents/adults with treatment recommendations being similar for the different age groups except for medications that are only approved for older subjects such as omalizumab. This is acknowledged but it may also be noted that the current treatment guidance in children is not clearly based on strong evidence as large studies investigating treatment responses to available CSU therapies in children are sparse. Thus, assuming similar disease pathology based on similar treatment guidance may not serve as strong argument for extrapolation. Overall, CSU in children is described as less severe and less refractory than adult CSU with overall shorter disease duration, higher response rates to antihistamines and lower incidence of angioedema and also antithyroid autoantibodies.

Of note, this variation only concerns the indication of children with treatment-refractory disease (i.e.. inadequate response to H1-antihistamines that are unexperienced to anti-IgE therapy); the same as for the approved adult/adolescent population (EMA/VR/0000257461). In children, this treatment-refractory population is less common as compared to adults given the less severe disease characteristics in the overall paediatric CSU population as described above. Based on available reports it approximately represents ~10 percent of children that are treated with high-dose antihistamines. From a mechanistical perspective it is reasonable to assume a similar immune pathology (potentially involving distinct CSU endotypes) leading to an insufficient response against antihistamines in both, children and adults. The extrapolation of efficacy from adults/adolescents to the proposed paediatric patient population is thus acceptable. Whether children with an inadequate response to antihistamines would show exactly the same response characteristics to dupilumab as seen for adults still harbours some remaining uncertainties which cannot be resolved with the limited clinical efficacy data provided, but this is not impacting on the conclusion that clinical relevant efficacy can be expected.

Given the limitations from the clinical study data, available exposure-response data in children with CSU can only be considered as supportive and appropriateness of the proposed paediatric dose regimens finally depends on PK simulations and matching resulting paediatric exposures with the adult population. The provided global paediatric popPK model describes the observed data in children with CSU acceptably well and is deemed qualified to predict PK in paediatric CSU patients and targeted exposures for the different doses are within an acceptable range (see PK/PD assessment in Section 2.3.4. for further details).

Claimed indication

The applicant proposes to extend the current indication for the treatment of adults and adolescents (EMA/VR/0000257461) to the treatment of children 2 years and older. This indication is agreed and the wording has been aligned with the one already used for the adult/adolescent population.

SmPC

The recommendation to consider discontinuation of treatment in case of no response and the periodically assessment for need of continued therapy as already included in section 4.2 of the PI in the adult/adolescent procedure do also strongly apply for the treatment of children with CSU. This is reflected in the SmPC.

2.4.4. Conclusions on the clinical efficacy

The clinical efficacy data obtained in study PKM16982 provide limited support for the intended extension of indication for the treatment of children aged 2 to 11 years with chronic spontaneous urticaria. Limitations mainly arise from the very small data set, differences in the severity of the

patient population of study PKM16982), and its uncontrolled design. Due to very limited paediatric data from EFC16461, studies A and C are not considered supportive.

The extension of indication ultimately relies on an extrapolation approach. A similar disease pathology in the claimed indication (children with CSU inadequately controlled by H1-antihistamines and naïve to anti-IgE therapy) can be assumed; thus extrapolation of efficacy from adults/adolescent to children is acceptable. Paediatric dose recommendations are based on exposure matching supported by popPK modelling and simulation. Also refer to Section 2.3.7. for more details.

The CHMP concluded that the efficacy data available for dupilumab in CSU (including extrapolation data and from adults and adolescents) supports the extension of indication of the adolescent and adult indication into children from 6 to 11. The indication is as follows:

Dupixent is indicated for the treatment of moderate to severe chronic spontaneous urticaria in adults, adolescents, and children (2 years and above) with inadequate response to H1 antihistamines and who are naive to anti-IgE therapy for CSU.

2.5. Clinical safety

Introduction

Overview of clinical studies

The results described in this Summary of Clinical Safety are based on the data from

- Study PKM16982 (15 participants) and
- Study EFC16461 Study A (2 participants) and Study C (3 participants), all <12 years of age.

See also Table 1 in section 2.3.1.

The studies were designed as outlined in section 2.4.

Safety parameters assessed and definitions In Study PKM16982, EFC16461 Study A, and EFC16461 Study C, the safety of dupilumab was evaluated based on the assessment of AEs, deaths, SAEs, AEs leading to permanent intervention discontinuation, AESIs, other selected AE groupings, chemistry and haematology laboratory results, vital signs, ECG results (EFC16461 Study A and Study C), and immunogenicity (i.e., ADA).

PCSAs were defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, and vital signs. Due to use of similar safety assessment strategies, below sections provide shared descriptions for all 3 studies with methodology differences highlighted.

Patient exposure

Disposition of study participants

Overall, in the dupilumab CSU Phase 3 program, 20 children aged ≥2 and <12 years were enrolled/randomized and exposed to the IMP. Of them, 18 received dupilumab.

Extent of exposure

Study PKM16982

In Study PKM16982, 15 children received dupilumab for 24 weeks at the following doses:

- 1 child with body weight ≥5 kg and <15 kg received dupilumab 200 mg q4w with no LD.
- 4 children with body weight ≥15 kg and <30 kg, aged ≥2 to <6 years old received dupilumab 300 mg q4w with no LD.
- 2 children with body weight ≥15 kg and <30 kg, aged ≥6 to <12 years old received dupilumab 300 mg q4w with an initial 600 mg LD.
- 8 children with body weight ≥30 kg and <60 kg received dupilumab 200 mg q2w with an initial 400 mg LD.

The duration of exposure to IMP (dupilumab) was similar in all age groups with a median duration of treatment exposure of 24 weeks. The majority of participants received study intervention for the entire 24-week treatment period, except 1 participant with body weight ≥15 kg and <30 kg, aged ≥2 to <6 years old receiving dupilumab 300 mg q4w with no LD who discontinued at Week 4.

EFC16461 Study A and Study C

The duration of exposure to IMP (dupilumab) was similar in all age groups with a median duration of treatment exposure of 24 weeks. The participant in Study C received dupilumab for 24 weeks while both participants in the Study A discontinued IMP after Week 10 and Week 4, respectively, with lack of efficacy as the reported reason for discontinuation (see EMA/VR/0000257461 EPAR on EMA website).

Demography

Study PKM16982

Of the 15 participants enrolled, 4 (26.7%) were ≥2 to <6 years old and 11 (73.3%) were ≥6 to <12 years old. The mean (SD) age of the participants was 6.7 (2.9) years with a range of 2 to 11 years, 73.3% were females. Most participants were White (60.0%), 26.7% were Asian, and 6.7% were Black or African American. Almost all (93.3%) were not Hispanic or Latino. The mean body weight at baseline was 28.94 kg, with 1 (6.7%) participant weighing <15 kg, 6 (40.0%) participants weighing ≥15 kg to <30 kg, and 8 (53.3%) participants weighing ≥30 kg.

EFC16461 Study A and Study C

All 5 children were ≥6 to <12 years old (range 8 to 11 years old). In the dupilumab groups, there were 2 male participants and 1 female participant; both participants from placebo group in the EFC16461 Study C were females. All 5 participants were White and not Hispanic or Latino. The baseline weight ranged from 32.5 to 55.7 kg.

Medical history and disease characteristics at baseline

Study PKM16982

Most participants had a history of at least 1 allergic comorbidity, including allergic rhinitis in 8 (53.3%) participants, asthma in 5 (33.3%) participants, food allergy in 4 (26.7%) participants, allergic conjunctivitis in 4 (26.7%) participants, and AD in 4 (26.7%) participants.

EFC16461 Study C and Study A

All 5 participants had a history of allergic comorbidities: allergic rhinitis, asthma, food allergy, allergic conjunctivitis, angioedema, and AD.

Relevant prior and concomitant medications

Study PKM16982

The most frequently reported prior medications included systemic H1-antihistamines in all 15 participants, ophthalmologicals in 12 (80.0%) participants, drugs for obstructive airway disease in 10 (66.7%) participants, corticosteroids, dermatological preparations in 6 (40.0%) participants, and systemic corticosteroids in 4 (26.7%) participants . All participants received concomitant systemic H1-antihistamines. Other frequently used concomitant medications by ATC class included ophthalmologicals in 12 (80%) participants, drugs for obstructive airway diseases in 10 (66.7%) participants, antibacterial for systemic use in 7 (46.7%) participants, corticosteroids, dermatological preparations in 6 (40.0%) participants, and nasal preparations in 6 (40.0%) participants. Of note, 5 (33.3%) of participants received concomitant systemic corticosteroids.

EFC16461 Study C and Study A

All 5 children received concomitant H1-antihistamines. For 1 child who received dupilumab in the EFC16461 Study A, the concomitant use of systemic corticosteroids was reported.

Adverse events

Overview

Study PKM16982

In Study PKM16982, at least 1 TEAE was reported in 12 (80.0%) participants and 3 (20.0%) participants experienced TEAEs that were considered as related to treatment by the Investigator. None of the TEAEs were assessed as severe. No deaths, SAEs, and no TEAEs leading to permanent study intervention discontinuation were reported in the study. No participants experienced any treatment-emergent AESIs.

EFC16461 Study C and Study A

Neither of the 2 children in the EFC16461 Study A had any TEAEs.

In the EFC16461 Study C, there were 2 TEAEs reported in 1 child from the placebo group (PTs: Tonsillitis streptococcal and Diarrhoea). There were no TEAEs reported in 1 child from the dupilumab group. In EFC16461 Study A and Study C, no deaths, no SAEs, no TEAEs leading to permanently study or intervention discontinuation, and no treatment-emergent AESIs were reported.

Common adverse events

In Study PKM16982, the most frequently reported TEAEs at the SOC level (≥2 participants overall) reported were as follows:

- Infections and infestations in 9 (60%) participants: 1 (100%) participant who received dupilumab 200 mg q4w, 2 (50.0%) participants who received dupilumab 300 mg q4w, 2 (100%) participants who received dupilumab 300 mg q4w with a LD of 600 mg, and 4 (50.0%) participants who received dupilumab 200 mg q2w with a LD of 400 mg.
- Gastrointestinal disorders in 4 (26.7%) participants: 1 (25.0%) participant who received dupilumab 300 mg q4w and 3 (37.5%) participants who received dupilumab 200 mg q2w with a LD of 400 mg.
- General disorders and administration site conditions in 2 (13.3%) participants: 2 (25.0%) participants who received dupilumab 200 mg q2w with a LD of 400 mg.

- Respiratory, thoracic and mediastinal disorders in 2 (13.3%) participants: 1 (100%) participant who received dupilumab 200 mg q4w and 1 (12.5%) participant who received dupilumab 200 mg q2w with a LD of 400 mg. At the PT level, TEAEs that occurred in more than 1 participant were Viral upper respiratory tract infection (4 [26.7%] participants), Influenza, Nasopharyngitis, and Vomiting (2 [13.3%] participants each).

Treatment-emergent treatment-related adverse events

Overall, 4 nonserious TEAEs of mild intensity reported by 3 participants were considered to be related to the IMP by the Investigator. These included PTs of Abdominal discomfort and Diarrhoea in the same participant, Insomnia, and Injection site reaction. None of the children in EFC16461 Study A and Study C had a TEAE considered to be related to the IMP by the Investigator.

Other adverse events

In Study PKM16982, 1 participant experienced a TEAE of Accidental overdose (8 days between 2 injections) that was nonserious and asymptomatic and 1 participant experienced a nonserious TEAE of Internal haemorrhage ("upper right arm internal bleeding [when measuring blood pressure]") of mild intensity.

Serious adverse event/deaths/other significant events

Deaths

There were no TEAEs leading to death reported for the children included in either Study PKM16982 or EFC16461 Study A and Study C.

Serious adverse events

There were no treatment-emergent SAEs reported for the children included in either Study PKM16982 or EFC16461 Studies A and Study C.

Adverse events of special interest (AESI)

Study PKM16982

There were no treatment-emergent AESIs. Treatment-emergent other selected AE grouping events were reported for 2 (25.0%) participants who received dupilumab 200 mg q2w with a LD of 400 mg: 1 participant experienced an injection site reaction and 1 participant had Conjunctivitis (PT: Conjunctivitis bacterial), both assessed as TEAEs of mild intensity.

EFC16461 Study A and Study C

There were no treatment-emergent AESIs or other selected AE grouping events reported for the children in EFC16461 Study A and Study C.

Laboratory findings

Haematology

No children in Study PKM16982, EFC16461 Study A and Study C experienced haematological abnormalities that were considered treatment-emergent SAEs or TEAEs leading to a permanent study intervention discontinuation.

Study PKM16982

There were no participants with PCSAs for red blood cells, platelets, and coagulation. Low WBCs were observed in 2 participants who received dupilumab 200 mg q2w with a LD of 400 mg. None of the changes were considered clinically significant or reported as AEs.

EFC16461 Study A and Study C

In EFC16461 Study A, 1 child who received dupilumab 200 mg q2w had a PCSA for low WBC count. In EFC16461 Study C, 1 child who received placebo had a PCSA for high haematocrit and 1 child who received dupilumab 300 mg q2w had a PCSA for high WBC count.

None of the changes were considered clinically significant or reported as AEs.

Clinical chemistry

Liver function

Study PKM16982

There were no participants with PCSAs for liver function parameters.

Study A and Study C

There were no children with PCSAs for liver function parameters in either of the studies.

Renal function

Study PKM16982

There were no clinically meaningful changes in renal function parameters observed in the study or PCSA reported as AEs. For 1 participant who received dupilumab 200 mg q2w with a LD of 400 mg, PCSA of urea nitrogen ≥ 6.4 mmol/L was observed.

EFC16461 Study A and Study C

There were no children with PCSAs for renal function parameters in either of the studies.

Metabolism and electrolytes

Study PKM16982

There were no participants with PCSAs for clinical chemistry laboratory parameters.

Study A and Study C

Among children in EFC16461 Study A and Study C, 1 participant from the placebo group had a PCSA for elevated potassium levels that was not considered clinically significant or reported as an AE. None of the other participants experienced a PCSA for clinical chemistry laboratory parameters.

Vital Signs

Study PKM16982

There were no clinically meaningful findings in the vital sign measurements and no reports of vital sign abnormalities as AEs. The most frequent PCSAs for vital sings was a low respiratory rate observed in following participants: 4 (100.0%) participants who received dupilumab 300 mg q4w without a LD, 1 (50.0%) participant who received dupilumab 300 mg q4w with a 600 mg LD, and 3 (37.5%) participants who received dupilumab 200 mg q2w with a LD of 400 mg.

There were few PCSAs identified for systolic or diastolic blood pressure or body weight. None of the participants experienced a PCSA for body temperature. A PCSA of weight reduction >5% was observed in one participant who received dupilumab 200 mg q2w with a 400 mg LD at Week 36. This was confirmed to be a data entry error at the study site and thus did not actually meet the PCSA criteria for weight decrease.

EFC16461 Study A and Study C

In EFC16461 Study A, 1 child who received dupilumab 200 mg q2w had a PCSA of low respiratory rate along with elevated systolic and diastolic blood pressure at baseline. In EFC16461 Study C, none of the children had a PCSA for vital signs.

Immunogenicity

None of the participants aged ≥2 to < 12 years with CSU developed a positive ADA response to dupilumab in Study PKM16982 or in EFC16461 Study A and Study C in children ≥2 to <12 years of age with CSU.

Safety in special populations

No new data available on intrinsic factors, extrinsic factors or drug interactions.

There were no pregnancies reported in children in either Study PKM16982 or EFC16461 Study A and Study C.

Overdose

In Study PKM16982, overdose was defined as any dose of IMP greater than twice the intended dose during an interval of less than 11 (for q2w regimen) or 25 (for q4w regimen) days; 1 participant who received dupilumab 200 mg q2w with a 400 mg LD had an Accidental overdose (8 days between 2 injections) that was nonserious and asymptomatic (5.3.5.2 PKM16982, Appendix 16.2.7 Adverse event data [16.2.7.4]). None of the children in EFC16461 Study A and Study C experienced an overdose (symptomatic or asymptomatic).

Safety related to drug-drug interactions and other interactions

See above.

Discontinuation due to adverse events

There were no TEAEs leading to permanent study discontinuation or study intervention discontinuation reported for the children included in either Study PKM16982 or EFC16461 Studies A and Study C.

Post marketing experience

Suspected unexpected serious adverse reactions and deaths from ongoing studies

During the review period from 01 October 2024 (cutoff date for SUSARs and deaths from the most recent marketing application for dupilumab) to 28 March 2025 (cutoff date of SUSARs and deaths for the current application), 1 new death but no new SUSARs were reported in Phase 2/3 and Phase 4 ongoing interventional studies. A new death was reported in Study LPS16676 which enrolled adult participants with Moderate-to-severe uncontrolled asthma. A female participant died due to respiratory insufficiency that was secondary to suspected chronic inflammatory polyneuropathy after more than 1

year of treatment with dupilumab and 16 days after the last dose. Both Investigator and Sponsor considered the event as not related to the study intervention.

Updates were received for 10 cases of death reported in prior review periods:

- For 2 cases of death reported in Study LPS16676 which enrolled adult participants with moderate-to-severe uncontrolled asthma, there were minor updates related to diagnostic procedures and course of events.
- For 8 cases of death reported in Study R668-BP-1902 which enrolled adult participants with bullous pemphigoid, CIOMS reports were updated following the study unblinding. No new safety concerns were identified from the review of the updated data.

Dupilumab was first approved by the US Food and Drug Administration on 28 March 2017 and by the EMA on 26 September 2017 for the treatment of adults with moderate-to-severe AD and has received subsequent approvals for both adult and paediatric patients for 4 indications (AD [6 months and older], asthma [6 years and older], EoE [1 year and older], and CSU [12 years and older]) and 3 indications in adults only (CRSwNP, PN, and COPD). No new safety concerns have been identified from the postmarketing data in the most recently submitted PSUR for dupilumab which covered the period from 29 March 2024 to 28 March 2025 (PSUSA/00010645/202503). Based on post-marketing surveillance through 28 March 2025, with a cumulative exposure of 2.7 million patient-years, the benefit-risk profile of dupilumab across all authorized indications remains favourable.

2.5.1. Discussion on clinical safety

Safety data evaluation is based on the results of two clinical studies, study PKM16982 (CUPIDKids) and study EFC16461 (CUPID) Study A and Study C that are all completed. Overall, 20 paediatric participants were enrolled, 18 participants were exposed to dupilumab and 2 to placebo.

In the PK/safety study PKM16982, uncontrolled safety data were collected over 24 (treatment phase) and 12 (safety follow-up phase) weeks in paediatric participants aged ≥ 2-12 years with CSU who remained symptomatic despite the use of H1-antihistamines. Here, 15 participants were enrolled and treated with dupilumab, with age and weight-based dose selection, most according to the approved AD posology apart from children with body weight ≥30 kg and <60 kg.

Further two studies A and C conducted under master protocol EFC16461 (CUPID) included 5 paediatric participants. Similarly, safety data were collected over 24 and 12 weeks, respectively, in paediatric participants with CSU who remained symptomatic despite the use of H1-antihistamines. 3 children received dupilumab, 2 received placebo.

Children were all aged ≥6 to <12 years.

The safety data results are thus obtained from a very small study population and are mainly uncontrolled.

Overall, in the dupilumab CSU Phase 3 program, 20 children aged ≥2 and <12 years were enrolled and exposed to the IMP. Of them, 18 received dupilumab.

Most participants in Study PKM16982 were exposed for ≥22 weeks, whereas only one participant of EFC16461 study C who was assigned to the dupilumab group was exposed for 24 weeks. Both participants of study A discontinued dupilumab treatment early, which reduces the truly exposed participants to 18, 16 thereof receiving dupilumab and 2 placebo.

The majority of the 15 participants in Study PKM16982 assigned to the dupilumab group experienced at least one TEAE, however, no participant in study EFC16461 Study A or Study C had any TEAE.

At the PT level, TEAEs that occurred in more than 1 participant in study PKM16982 were viral upper respiratory tract infection, influenza, nasopharyngitis, and vomiting; all other TEAEs occurred individually. All observed TEAEs are qualitatively characteristic of the studied age group apart from internal haemorrhage, which means bruise of the upper limb after measuring blood pressure; this patient received antihaemorrhagic medication.

In Study PKM16982, 4 TEAEs observed in 3 participants including PTs of insomnia, abdominal discomfort, diarrhoea, and injection site reaction were considered to be related to the IMP by the Investigator.

Both AESI observed in Study PKM16982 are known AESI and listed as ADR in the SmPC (injection site reaction and conjunctivitis).

No changes in haematology or clinical chemistry parameters were considered clinically significant or reported as AEs. Vital signs were overall clinically unremarkable.

None of the participants aged ≥2 to < 12 years with CSU developed a positive ADA response to dupilumab. No participant discontinued dupilumab due to TEAEs.

As mentioned above, the participant number is not considered representative to allow a dedicated analysis of the safety data in this indication and age group. It is acknowledged that participant enrolment in this age group is difficult due to the epidemiology of CSU, which is reflected by sample size estimation included in the respective PIP. Interpretation of the study results is thus a matter of contextualisation with the overall existing safety data base in paediatric participants. The submitted data do not give cause for safety concerns and do not differ from other indications in this age group.

2.5.2. Conclusions on clinical safety

There were no new safety issues observed in both studies PKM16982 and EFC16461 study A and C. The safety profile in children aged ≥ 2-12 years with CSU remains favourable. However, considering the uncontrolled data collected in a numerically limited patient population emphasises the importance of a reliable extrapolation approach.

Based on available data there is no indication that the higher exposure seen with the chosen paediatric dose regimens has an impact on dupilumab's safety profile, knowing that the highest predicted exposure reached with this dosing regimen is already approved in AD in the same age group.

The SmPC is considered appropriate.

The CHMP concluded that the safety profile of dupilumab for the treatment of moderate to severe CSU in children aged 2 to 11 years whose disease is inadequately controlled by H1 antihistamines and who are naive to anti-IgE therapy for CSU is considered acceptable.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted two updated RMP versions with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan: the PRAC considered that the risk management plan version 14.1 is acceptable.

The CHMP endorsed this advice without changes. The CHMP endorsed the Risk Management Plan version 14.1 with the following content:

Safety concerns

Table 21. Summary of the safety concerns

Important identified risk	Systemic hypersensitivity (including events associated with immunogenicity)
Important potential risk	None
Missing information	Use in pregnant and lactating women
	Long-term safety in paediatric patients

Pharmacovigilance plan

Table 22. Ongoing and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1- Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2- Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3- Required additional pharmacovigilance activities				
Pregnancy registry (R668-AD-1639) Ongoing	To evaluate the effect of exposure to dupilumab on pregnancy and infant outcomes.	Use in pregnant and lactating women	Protocol submission	Submitted to PRAC in Jan-2018 (and amendment #1 in Sep-2018)
			Amended protocol (asthma cohorts)	Submitted for information with EU-RMP v5.0
			Final report	Jan-2027
Pregnancy Outcomes Database Study (R668-AD-1760) Ongoing	To measure the prevalence of adverse pregnancy and infant outcomes in a cohort of women with AD exposed to dupilumab during pregnancy	Use in pregnant and lactating women	Protocol submission (amendment 1)	Submitted for information with EU-RMP v5.0
			Amendment 3	Submitted for information with

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	compared to a disease-matched cohort exposed to systemic medication or phototherapy (but unexposed to dupilumab) in AD patients and a disease-matched cohort who were not exposed to these treatments during pregnancy.			EU-RMP v14.0
			Final report	Apr-2027
An open-label extension study to assess the long-term safety of dupilumab in patients ≥6 months to <18 years of age with AD (Phase III) (LTS1434) (R668-AD-1434) Ongoing	To assess the long-term safety of dupilumab in pediatric patients with AD.	Long-term safety of dupilumab in pediatric patients with AD	Final report	Q4 2027
A registry-based non-interventio nal post-authorizati on safety study to evaluate the long-term safety of dupilumab in children aged ≥6 months to <6 years with moderate-to-severe atopic dermatitis using the PEDISTAD registry: a cohort design CSA0014 Ongoing	To assess the long-term safety of dupilumab in pediatric patients with moderate-to-sev ere AD.	Long-term safety of dupilumab in paediatric patients (≥6 months to <6 ye ars) with AD	Synopsis v1.0 provided in Annex 3.1 of EU-RMP submitted within procedure EMEA/H/C/004390/II/0 060	
			Protocol submitted to PRAC on	18-Sep-202 3
			Protocol approved by PRAC on	
			Annual progress report	14-Dec-2023
			Final Report	Q4 2024-20 30
				Q4 2024 report submitted on 18-Dec-202 4
				Q3 2032

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates

AD: Atopic Dermatitis; EMEA: European Medicines Agency; EU: European Union; PRAC: Pharmacovigilance Risk Assessment Committee; Q: Quarter; RMP: Risk Management Plan.

Risk minimisation measures

Table 23. Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Systemic hypersensitivity (including events associated with immunogenicity)	**Routine risk minimization measures:** • SmPC sections 4.3, 4.4 and 4.8 • PIL sections 2 and 4 • Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Hypersensitivity questionnaire **Additional pharmacovigilance activities:** None
Use in pregnant and lactating women	**Routine risk minimization measures:** • SmPC sections 4.6 and 5.3 • PIL section 2 • Prescription only medicine A**dditional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Pregnancy questionnaire **Additional pharmacovigilance activities:** • Pregnancy registry study (R668-AD-1639), • Pregnancy Outcomes Database Study (R668-AD-1760)
Long-term safety in paediatric patients	**Routine risk minimization measures:** Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:**

Safety concern	Risk minimization measures	Pharmacovigilance activities
		LTS1434 (R668-AD-1434) and DUPI PEDISTAD registry-based study (CSA0014)

PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, which were reviewed and accepted by the CHMP. In addition, the list of local representatives in the PL has been revised to delete the contact details for the representatives of the United Kingdom (Northern Ireland).

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Chronic spontaneous urticaria (CSU), also known as chronic idiopathic urticaria, is characterized by the spontaneous appearance of pruritic wheals (hives) and flare-type skin reactions without a specific known cause that persists for more than 6 weeks, and which may be accompanied by angioedema. Wheals and pruritus represent the key urticaria symptoms. Owing to the unpredictability of the occurrence of pruritic wheals, the disease can have a substantial impact on patients' daily life. Significant exacerbations of chronic urticaria may result in emergency room visits and hospitalizations. CSU is a globally prevalent, debilitating skin condition that affects both adults and children. The disease can develop at any age, but is rarely diagnosed before the age of 2 years and is less common in children as in adults with a peak incidence between 20 and 40 years.

3.1.2. Available therapies and unmet medical need

The treatment approaches for CSU in children (<12 years of age) are similar to adults and adolescents. However, importantly, biologics are not approved for treatment of CSU in children aged <12 years. The updated international guidelines[4] recommend a stepwise treatment approach. Step 1 treatment starts with non-sedating H1-antihistamines at approved doses. If symptoms are inadequately controlled after 2 to 4 weeks, an increase in H1-antihistamine dose up to 4-fold (unapproved dose) is recommended (Step 2). If symptoms remain uncontrolled or intolerable, omalizumab (anti-IgE) should be added in patients >12 years of age (Step 3). Of note, Step 3 does not apply for children <12 years of age.

[4] (Zuberbier et al., 2022)

Beyond this, Step 4 treatment options include add-on ciclosporin A, or montelukast (leukotriene receptor antagonist) to H1 antihistamines.

Based on a limited number of reports, approximately 10% of children on high-dose H1-antihistamines still remain symptomatic. There are no approved biologic therapies for children with an age below 12 years. Off-label cyclosporine is recommended in clinical guidelines but has a high incidence of dose dependent adverse effects. Other alternative agents such as antidepressant and immunosuppressants have little data on efficacy. There is thus a substantial therapeutic need for new therapeutic options in children <12 years of age with CSU who are refractory to antihistamine treatment.

3.1.3. Main clinical studies

The paediatric clinical development program for dupilumab in CSU in children aged ≥2 to <12 years is based on an extrapolation approach supported by 3 clinical studies. A phase 3 PK/safety Study PKM16982 including 15 children (≥2 to <12 years of age) and additional data obtained from 5 children (≥6 to <12 years of age) enrolled in the phase 3 studies EFC16461 (Study A & C). All studies enrolled children with CSU with an inadequate response to antihistamines. Depending on the participant's weight that was planned to be in the range between 5 and 60 kg, dupilumab was given at 200 mg q4w, 300 mg q4w, or 200 mg q2w. Dose regimens for participants above 15 kg with an age ≥6 years included a loading dose. Participants were treated for 24-weeks. In addition, popPK modelling and simulation approaches for the proposed dose regimens were utilized to support the extrapolation approach. The latter phase 3 studies also enrolled adult and adolescent patients and represent the base for the efficacy claims in the older age population as assessed in EMA/VR/0000257461.

3.2. Favourable effects

In study PKM16982, the mean numerical improvement in the modified UAS7 at week 24 was -9.5 points (standard deviation: 8.0). Symptom improvements observed were diverse (min/max: -23 to -1 in mUAS7), similar to what has been observed for the adult/adolescent CSU population. In the 10 participants with available mUAS7 data, there was no worsening of symptoms under treatment with dupilumab. Similar trends for improvements were observed for change from baseline in C-DLQI (evaluated in children ≥ 4 years; n=11).

The proposed dose regimen resulted in dupilumab concentrations in children with CSU that were within the range of mean concentrations obtained in other approved paediatric indications that have been established as safe in adults and adolescents.

3.3. Uncertainties and limitations about favourable effects

The provided clinical efficacy data are largely limited due to the very small data set obtained in children with CSU and the uncontrolled design of study PKM16982. Only descriptive analyses can be made. The number of PK observations in children with CSU was very limited (n=50 from 18 children). Only 1 patient at the upper weight limit was included in the 200 mg q4w dosing group.

The treatment effect seen for dupilumab in the adult/adolescent population (≥ 12 years) can be extrapolated to children aged 2-11 years as the CSU immune pathology in the patient population covered by the indication (patients with an inadequate antihistamine response) is assumed similar between children and adults/adolescents.

Efficacy claims rely on an extrapolation approach with dose recommendations based on popPK modelling and exposure matching. The provided global paediatric popPK model is deemed qualified to predict PK in paediatric CSU patients.

3.4. Unfavourable effects

In Study PKM16982, at least 1 TEAE was reported in 12 (80.0%) participants and 3 (20.0%) participants experienced TEAEs that were considered as related to treatment by the Investigator: 4 TEAEs reported in 3 participants by PTs of insomnia, abdominal discomfort and diarrhoea, and injection site reaction.

At PT level, TEAEs that occurred in more than 1 participant were viral upper respiratory tract infection (4 [26.7%] participants), influenza, nasopharyngitis, and vomiting (2 [13.3%] participants each).

Neither of the 2 children in the EFC16461 Study A had any TEAEs and there were no TEAEs reported in 1 child from the dupilumab group.

No ADA responses were observed in any of the study participants.

3.5. Uncertainties and limitations about unfavourable effects

Participant numbers were very limited. The majority of the safety data come from a PK/safety study and are uncontrolled.

In studies PKM16982 none of the TEAEs were assessed as severe. No deaths, SAEs, and no TEAEs leading to permanent study intervention discontinuation were reported in the study.

No participants experienced any treatment-emergent AESIs.

At PT level, no unusual TEAEs were observed, all TEAE were typical for the studied age group.

3.6. Effects Table

Table 24. Effects Table for Dupixent in children ≥2 to <12 years with Chronic Spontaneous Urticaria (data cut-off PKM16982: 28 Feb 2025)

Effect	Short description	Unit	Treatment*[1]	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
mUAS7	Change from baseline in UAS7 at Week 24	Pts.	-9.5	N/A	▪ Only 10 participants with available mUAS7 data ▪ Uncontrolled ▪ Improvements similar to control-arm of the adult studies ▪ Descriptive data only ▪ The claim for efficacy ultimately relies on extrapolation with modelling-based exposure matching	PKM16982
Unfavourable Effects						
TEAE	Participant with any TEAE	%	80.0	N/A	mild-to-moderate, transient, common for age group	PKM16982*[2]

Effect	Short description	Unit	Treatment*1	Control	Uncertainties / Strength of evidence	References
SAE	Serious TEAE	%	0	N/A		idem
Death		%	0	N/A		idem
Immunogenicity	Positive ADA response	%	0	N/A		idem

Abbreviations: ADA: antidrug antibodies, Pts: points, SAE: serious adverse events, TEAE: treatment-emergent adverse events, mUAS7: modified urticarial activity score over 7 days

Notes: *1 200 mg q4w, 300 mg q4w, or 200 mg q2w doses depending on participant's weight with a loading dose for participants above 15 kg and ≥6 years. *2 Neither of the 2 children in EFC16461 Study A had any TEAEs. In EFC16461 Study C, there were 2 TEAEs reported in 1 child from the placebo group (PTs: Tonsillitis streptococcal and Diarrhea). There were no TEAEs reported in 1 child from the dupilumab group.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

CSU has a profound impact on children's quality-of-life including anxiety and psychological symptoms. Based on available literature, approximately ~10% of children on high-dose H1-antihistamines still remain symptomatic. This represents a smaller patient subset as compared to the adult/adolescent CSU disease. Still, approved treatment options are very limited for this antihistamine-refractory paediatric CSU population.

The paediatric clinical development program for Dupixent in children with CSU aged ≥2 to <12 years, weighing at least 5 kg, was based on an extrapolation approach that considers PK and response (efficacy) data in paediatric CSU patients as well as analyses that should support the assumption of similar exposure-response relationship in children aged ≥2 to <12 years and adult/adolescent patients with CSU. During the procedure, the assumption of similar exposure-response relationship was insufficiently supported by available data, thus an extrapolation approach based on exposure matching was adopted.

A similar clinical pathology between adults and children in the claimed indication (children with CSU inadequately controlled by H1-antihistamines and naïve to anti-IgE therapy) can be assumed. Symptom improvements by means of mUAS7 and quality-of-life measures seen in the clinical trials in children with CSU do provide some support. Relevant limitations including the very low number of children included in the paediatric CSU studies, and the uncontrolled study design of the main PK study need to be noted which largely limit direct comparisons with the adult/adolescent CSU population. Whether children with an inadequate response to antihistamines would show exactly the same response characteristics to dupilumab as seen for adults still harbours some remaining uncertainties which cannot be resolved with the limited clinical efficacy data provided, but this is not impacting on the conclusion that clinical relevant efficacy is expected.

The extrapolation approach in children aged ≥2 to 11 years of age with CSU weighing at least 5 kg is further based on exposure matching. A global paediatric popPK model was developed that was based on all available paediatric PK data from previously approved paediatric indications for dupilumab in children. This global paediatric popPK model described the observed data in children with CSU acceptably well and is deemed qualified to predict PK in paediatric CSU patients.

The observed dupilumab trough concentrations as well as popPK predicted exposure obtained by the chosen dosing regimens in children with CSU were above an exposure level proven to be efficacious in adults with CSU. Paediatric exposure of dupilumab is predicted to be near the upper limit of what has been established as safe in adults/adolescents. However, the dosing regimen resulting in highest predicted exposure is already approved in AD in the here proposed age group. It is therefore reassuring that no exposure-related increases in adverse events were identified in children with AD. Furthermore, there were no significant unfavourable effects in children with CSU, only a few TEAEs were observed in the PK study that do not deviate from the hitherto known safety profile of dupilumab in paediatric patients younger than 12 years. Thus, based on available data, there is no indication that the higher exposure seen with the chosen paediatric dose regimens has an impact on dupilumab's safety profile.

Overall, the provided data support the extrapolation of efficacy and do not raise a safety concern for the proposed dupilumab dosing regimens in the paediatric target population (2-11 years of age, weighing at least 5 kg).

3.7.2. Balance of benefits and risks

A therapeutic need for new therapeutic options in children <12 years of age with CSU with an inadequate response to antihistamine treatment is acknowledged by the CHMP.

The efficacy for the treatment of moderate to severe chronic spontaneous urticaria in children (2-11 years of age) with inadequate response to H1 antihistamines and who are naive to anti-IgE therapy for CSU is extrapolated from patients above 12 years with paediatric doses derived by popPK modelling and exposure matching. Overall, the provided data support the extrapolation of efficacy in children 2-11 years old.

The provided safety data obtained in children 2-11 years old with CSU appear consistent with the hitherto known safety profile of dupilumab. Furthermore, based on available data there is no indication that the higher exposure seen with the chosen paediatric dose regimens has an impact on dupilumab's safety profile, knowing that the highest predicted exposure reached with this dosing regimen is already approved in AD in the same age group. This gives sufficient assurance on an acceptable safety profile, even bearing in mind the very limited number of patients.

A positive benefit / risk ratio can be concluded.

3.7.3. Additional considerations on the benefit-risk balance

None.

3.8. Conclusions

The overall B/R of Dupixent is positive in the following indication:

Dupixent is indicated for the treatment of moderate to severe chronic spontaneous urticaria in adults, adolescents, and children (2 years and above) with inadequate response to H1 antihistamines and who are naive to anti-IgE therapy for CSU.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II	I, and IIIB

Extension of indication to include treatment of moderate to severe chronic spontaneous urticaria (CSU) in children aged 2 to 11 years with inadequate response to H1 antihistamines and who are naive to anti-IgE therapy for CSU. This is based on the results from study PKM16982: a multi-center, single-arm study to investigate the pharmacokinetics and safety of dupilumab in male and female participants ≥2 years to <12 years of age with uncontrolled chronic spontaneous urticaria (CSU). Consequently, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 14.1 of the RMP is approved. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template.

The variation led to amendments to the annexes I, and IIIB and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB, and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0353/2024 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the "EPAR-Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Dupixent-H-C-4390-II-EMAVR0000282164'

Attachments

1. SmPC and Package Leaflet (changes highlighted) as adopted by the CHMP on 26 Feb 2026.