18 February 2025
EMA/67383/2025
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

Dupixent

International non-proprietary name: Dupilumab

Procedure No. EMEA/H/C/004390/II/0083

Note

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

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The PRAC/CHMP Rapporteurs should complete the 'actual' date at each stage of the procedure. This is the date of circulation of the report to CHMP/PRAC members.

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	02 Mar 2024	02 Mar 2024	☐
☐	CHMP Rapporteur Assessment Report	26 Apr 2024	26 Apr 2024	☐
☐	PRAC Rapporteur Assessment Report	03 May 2024	03 May 2024	☐
☐	PRAC members comments	07 May 2024	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	08 May 2024	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	16 May 2024	16 May 2024	☐
☐	CHMP members comments	21 May 2024	17 May 2024	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 May 2024	24 May 2024	☐
☐	Request for supplementary information	30 May 2024	30 May 2024	☐
☐	Submission of MAH responses	19 Jul 2024	18 Jul 2024	☐
☐	Start of procedure	22 Jul 2024	22 Jul 2024	☐
☐	CHMP Rapporteur Assessment Report	20 Aug 2024	22 Aug 2024	☐
☐	PRAC Rapporteur Assessment Report	23 Aug 2024	23 Aug 2024	☐
☐	PRAC members comments	28 Aug 2024	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	29 Aug 2024	29 Aug 2024	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	05 Sep 2024	05 Sep 2024	☐
☐	CHMP members comments	09 Sep 2024	09 Sep 2024	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	12 Sep 2024	13 Sep 2024	☐
☐	Request for supplementary information	19 Sep 2024	19 Sep 2024	☐
☐	Submission of MAH responses	29 Nov 2024	28 Nov 2024	☐
☐	Start of procedure	02 Dec 2024	02 Dec 2024	☐
☐	CHMP Rapporteur Assessment Report	06 Jan 2025	06 Jan 2025	☐
☐	CHMP members comments	20 Jan 2025	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	23 Jan 2025	n/a	☐
☒	Request for supplementary information	30 Jan 2025	30 Jan 2025	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Criteria for PRAC plenary discussion: proposal for update of SmPC/PL, introduction of or changes to imposed conditions or additional risk minimisation measures (except for generics aligning with the originator medicinal product), substantial changes to the pharmacovigilance plan (relating to additional pharmacovigilance activities, except for generics adapting aligning with the originator medicinal product), substantial disagreement between the Rapporteur and other PRAC members, at the request of the Rapporteur, any other PRAC member, the Chair or EMA.

[3] Sections related to Risk Management Plan or on non-interventional PASS results. If PRAC advice was ad hoc requested by the CHMP, the relevant Attachment to the assessment report applies and has been endorsed by the PRAC.

Procedure resources	
CHMP Rapporteur:	Jan Mueller-Berghaus

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List of abbreviations

AD	atopic dermatitis
ADA	anti-drug antibody
ADR	adverse drug reaction
AAS7	angioedema activity score over 7 days
AE	adverse event
AESI	adverse event of special interest
CI	confidence interval
CMQ	custom MedDRA query
COVID-19	coronavirus disease 2019
CRSwNP	chronic rhinosinusitis with nasal polyps
CSU	chronic spontaneous urticaria
ECG	electrocardiogram
EoE	eosinophilic esophagitis
EOS	end of study
EOT	end of treatment
FDA	Food and Drug Administration
HLGT	high-level group term
HLT	high-level term
HSS7	hives severity score over 7 days
IgE	immunoglobulin E
IgG	immunoglobulin G
IL	interleukin
ISS7	itch severity score over 7 days
ITT	intent-to-treat
kg	kilograms
LLT	lower-level term
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimal important difference
NAb	neutralizing antibody
NC	not calculable
OCS	oral corticosteroids
PCSA	potentially clinically significant abnormality
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PN	prurigo nodularis
PT	preferred term
PY	patient-years
q4w	every 4 weeks
qw	once a week
SAE	serious adverse event
SC	subcutaneous
SOC	system organ class
TEAE	treatment-emergent adverse event
UAS7	urticaria activity score over 7 days
UCT	urticaria control test
US	Unites States

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Sanofi Winthrop Industrie submitted to the European Medicines Agency on 13 February 2024 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of moderate to severe chronic spontaneous urticaria in adults and adolescents 12 years and older, who are symptomatic despite treatment with H1 antihistamines and who are intolerant to or inadequately controlled by anti-IgE therapy for Dupixent, based on the results from studies EFC16461 (CUPID) study B (pivotal) and study A (supportive); EFC16461 Study B was a 24-week, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of dupilumab in adult and adolescent participants with CSU who remained symptomatic despite the use of H1-antihistamine and who were intolerant or incomplete responders to omalizumab and EFC16461 Study A was a 24-week, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of dupilumab in participants with CSU who remained symptomatic despite the use of H1-antihistamine and who were naïve to omalizumab. As a consequence, 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 11.0 of the RMP has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0297/2023 on the acceptance of a modification of an agreed paediatric investigation plan for dupilumab

(Dupixent), (EMEA-001501-PIP07-20-M01) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council.

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Sanofi Winthrop Industrie submitted to the European Medicines Agency an application for modification of the agreed paediatric investigation plan with a deferral and a waiver as set out in the European Medicines Agency's decision P/0153/2021.

At the time of submission of the application, the PIP P/0297/2023 was completed (see partial compliance report).

Information relating to orphan market exclusivity

N/A

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.

Scientific advice

The MAH received Scientific Advice from the CHMP on 26 March 2020 (EMEA/H/SA/2744/10/2020/II). The advice pertained questions concerning the clinical development program (study A and B of master protocol EFC16461) for Chronic Spontaneous Urticaria.

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 proposed for this submission is as follows:

Dupixent is indicated for the treatment of moderate-to-severe chronic spontaneous urticaria in adults and adolescents (12 years and older), who are symptomatic despite treatment with H1antihistamines and who are intolerant to or inadequately controlled by anti-IgE therapy.

Epidemiology and risk factors

The prevalence and incidence of CSU are not precisely known and show considerable regional differences. 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). Epidemiologic data for CSU in the adolescent population is currently sparse; similar point prevalence estimates as for adults have been reported. Women are more frequently affected than men (approximately 70% of cases), although no sex-specific difference is reported in patients below 15 years of age.

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

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 similar in adults and adolescents. 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.

Skin biopsies from patients with CSU have been shown to have an eosinophilic and T-helper (Th)2 immunopathology. IL-4 levels have been reported to be elevated in the serum of patients with CSU. The Th2 cytokines IL-4 and IL-13 promote isotype class switching to IgE and act on mast cells, eosinophils, and basophils. IL-4, and to a lesser extent IL-13, via IL4Rα receptor can directly increase FcεRIα expression on mast cells and basophils, potentially priming these cells for allergen-induced activation. Preclinical data suggest that dupilumab inhibits the IL-4 mediated induction of B cell to plasma cell subclass switching from IgM to IgE, with consequent IgE lowering leading to reduction of FcεRIα expression. IL-4 and IL-13 can also induce IgE-dependent and IgE-independent gene expression changes in mast cells.

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 may be accompanied by angioedema. CSU needs to be differentiated from other medical conditions where wheals, angioedema, or both can occur, for example anaphylaxis, autoimmune disorders, urticarial vasculitis, or bradykinin-mediated angioedema including hereditary angioedema. The diagnosis of CSU is based on a detailed patient 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). Basic tests include a differential blood count and CRP and/or ESR, in all patients, and total IgE and anti-TPO, in patients in specialist care and can help to identify indicators for autoimmune CSU. The diagnostic approaches for CSU in adults and adolescents are similar.

Management

The therapeutic goal in the treatment of CSU is to achieve complete freedom of symptoms. The current international guideline for urticaria) recommends a 4-step treatment approach for disease management (Zuberbier et al., 2022). The treatment algorithm in the guideline is the same for adult and adolescent patients. Step 1 starts with non-sedating H1-antihistamines at approved 'standard' 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 still remain uncontrolled or are intolerable, omalizumab (anti-IgE) should be added (Step 3). Beyond this, Step 4 treatment options include add-on ciclosporin A, or montelukast (leukotriene receptor antagonist) to H1-antihistamine. In case of acute exacerbations, treatment with sufficient doses of oral glucocorticoids can be given for a short period (up to a maximum of ten days) to reduce the duration and activity of the disease.

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

Unmet medical need

The burden for CSU patients is substantial, especially for patients with persistent recalcitrant disease that is inadequately controlled with currently recommended treatment options (e.g. H1-antihistamines and anti-IgE therapy). Approximately 30-50% of patients treated with high-dose antihistamines still remain symptomatic. For these patients, anti-IgE treatment with omalizumab is the only approved treatment which is effective in a substantial proportion of patients, while a distinct number of patients remain uncontrolled. For this omalizumab refractory population, off-label cyclosporine is recommended but has limited efficacy and is associated with a high incidence of adverse reactions.

New treatment option for patients who are intolerant or incomplete responders to anti-IgE therapy are needed.

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

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

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 h(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.

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

Paediatric investigation plan

On 17 March 2023 the applicant submitted to the European Medicines Agency a request for a modification of the agreed Paediatric Investigation Plan as set out in the Agency's decision P/0153/2021 issued on 16 April 2021 on the basis that the applicant encountered difficulties with its implementation. The proposed indication is "Treatment of chronic spontaneous urticaria (CSU) in patients aged 12 years and older whose disease is not adequately controlled with H1 antihistamine and an anti-IgE antibody treatment". The reasons for applying the PIP modification are as follows:

The currently agreed measures of PIP 001501-PIP07-20 consist of three studies:

- **Study 1 (EFC16461)** consists of two independent phase 3, 24-week, randomized, double-blind, placebo-controlled studies covered by the same master protocol EFC16461
  - **Study A** assesses the efficacy and safety of dupilumab in adults, adolescents (≥12 to <18 years), and children (≥6 to <12 years) with CSU who remain symptomatic despite the use of H1-antihistamine treatment
  - **Study B** assesses the efficacy and safety of dupilumab in adults and adolescents (≥12 to <18 years) with CSU who remain symptomatic despite the use of H1-antihistamine treatment and are intolerant or incomplete responders to omalizumab.
- Study 2 (PKM16982) consists of an open-label, single-arm study to evaluate pharmacokinetics and safety of dupilumab in children from 2 years to less than 12 years of age with chronic spontaneous urticaria.
- Study 3 consists of an extrapolation of the data generated from the adult and adolescent to the paediatric population.

The proposed PIP modification includes a revision of the agreed measures of Study 1 (EFC16461) as the Applicant has encountered significant challenges in recruiting/enrolling paediatric participants in Study 1 (Study A and Study B). Therefore, an update of participant numbers included in the Study 1 was requested to reflect the number actually enrolled in both Studies A and B. The proposed PIP modification also includes an update of the measures of Study 2 (PK/Safety study) and Study 3 (extrapolation). As to the planned participant numbers, a total of 10 adolescent patients (≥12 to <18 years old) were originally planned to be enrolled in the CSU phase 3 dupilumab program which were then reduced to 8 participants. PDCO accepted the retrospective modification as Study 1 had already been completed.

It is noteworthy that the Phase 3 study evaluating Dupixent in Chronic Inducible Cold Urticaria (LIBERTY-CINDU) did not meet the required efficacy endpoints to continue this program (Sanofi Press release 27.04.2023).

2.1.4. General comments on compliance with GCP

N/A

2.2. Quality/Non-clinical aspects

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

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, dupilumab is not expected to pose a risk to the environment. The justification for not conducting ERA studies is 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 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 new CSU indication is supported by existing usability data for the authorized presentations. Therefore, 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

Study number/ status	Study objective	Treatment/ follow-up duration	Participants randomized/ treated
Phase 3			
EFC16461 (CUPID) Study B Completed 5.3.5.1 [EFC16461 Study B]	Efficacy and safety of dupilumab compared to placebo in omalizumab intolerant or incomplete responder participants with CSU who remain symptomatic despite the use of H1-antihistamines. (Primary endpoint: Change from baseline in UAS7 [composite patient reported itch and hive score] at Week 24. Main key secondary endpoint: Change from baseline in ISS7 at Week 24).	24/12 weeks	Randomized/treated: 108/108 (Dupilumab: 54[a], Placebo: 54[a])
EFC16461 (CUPID) Study A Completed 5.3.5.1 [EFC16461 Study A]	Efficacy and safety of dupilumab compared to placebo in participants with CSU who remain symptomatic despite the use of H1-antihistamines. (Primary endpoint: Change from baseline in UAS7 [composite patient reported itch and hive score] at Week 24. Main key secondary endpoint: Change from baseline in ISS7 at Week 24).	24/12 weeks	Randomized/treated: 138/138 (Dupilumab: 70[a], Placebo: 68[a])

CSU: Chronic spontaneous urticaria; ISS7: Itch severity score over 7 days; UAS7: Urticaria activity score over 7 days.
a As treated

2.3.2. Pharmacokinetics

The Applicant is seeking the approval of DUPIXENT® (dupilumab) for the treatment of moderate to severe chronic spontaneous urticaria (CSU) in adults and adolescents 12 years and older, who are symptomatic despite treatment with H1 antihistamines and who are intolerant to or inadequately controlled by anti-IgE therapy. Pharmacokinetic (PK), pharmacodynamic (PD) and immunogenicity data were collected in the two Phase 3 studies in patients with CSU (EFC16461 Study A and Study B). Table 1 shows a summary of these studies.

Table 1. Summary of clinical studies included in study POH0861

Phase	Study	Dose Regimen	Duration of Treatment	Population	PK Sampling	N[a]	Current Status
3	EFC16461 Study A	**Adults (regardless body weight) and adolescents weight ≥60 kg:** SC 300 mg q2w with 600 mg loading dose **Adolescents weight <60 kg and children ≥6 to <12 years of age and weight ≥30 kg:** SC 200 mg q2w with 400 mg loading dose **Children ≥6 to <12 years of age and weight <30 kg and ≥15 kg:** SC 300 mg q4w with 600 mg loading dose[b]	24 weeks	Adults, adolescents, and children with CSU	Sparse sampling[c]	70	Completed
3	EFC16461 Study B	**Adults (regardless body weight) and adolescents weight ≥60 kg:** SC 300 mg q2w with 600 mg loading dose **Adolescents weight <60 kg:** SC 200 mg q2w with 400 mg loading dose	24 weeks	Adults and adolescents with CSU	Sparse sampling[c]	54	Completed

Abbreviation: CSU: chronic spontaneous urticaria; q2w: every two weeks.

a. Total number of participants in EFC16461 Study A was 138. 70 participants (~50% of total participants) were randomly assigned to be exposed to dupilumab. Participants enrolled in the dupilumab treatment group were 66 adults and 1 adolescent with weight ≥60 kg, 1 adolescent with weight <60 kg and 2 children ≥6 to <12 years of age with weight ≥30 kg. No participant enrolled was ≥6 to <12 years of age with weight <30 kg and ≥15 kg.
Total number of participants in EFC16461 Study B was 108. 54 participants (~50% of total participants) were randomly assigned to be exposed to dupilumab.

b. No CSU patient received 300 mg q4w in EFC16461 Study A. 300 mg q4w dosing regimen is to be studied in future CSU study.

c. Scheduled PK sampling at baseline, trough at Weeks 12, and 24 during treatment, and at Week 36 during safety follow-up period.

Overall, dupilumab exhibits nonlinear PK, where concentration-dependent target-mediated clearance predominates at low concentration range and linear elimination pathway predominates at concentrations above the target saturating level. Similar dupilumab PK profiles (mean concentration over time) were observed across healthy volunteers (HV), atopic dermatitis (AD), asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), Prurigo Nodularis (PN) and Eosinophilic Esophagitis (EoE) adult populations (studies R668-MX-16103-CP-01V1, POH0530, POH0668 and POH0611, POH0779 and R668-PK-1229-SR-01V1).

A global population PK (Pop PK) base model of dupilumab was previously developed to harmonise the modelling work for future indications, based on the knowledge gained from PK analysis in adult HV, AD and asthma patients (including PK similarity, same base model structure, and body weight as the primary source of PK variability). This global Pop PK base model of dupilumab was developed with pooled data from six Phase 1 trials in healthy adults, ten Phase 1, 2 and 3 trials in adult patients with AD (R668-MX-16103-CP-01v1), and four Phase 2 and 3 trials in adult and adolescent patients with asthma (POH0530). Dupilumab PK was adequately characterised by this global model consisting of a two-compartment model with first-order absorption, parallel linear and Michaelis-Menten (M-M) elimination, and body weight as a covariate (Study POH0668, previously submitted in the supplemental application for CRSwNP).

Dupilumab is administered by subcutaneous (SC) injection. The proposed dupilumab SC dose regimens for patients with CSU, which are approved dose regimens for AD, are as follows:

- 300 mg q2w with a loading dose of 600 mg for adults (≥18 years of age),
- 300 mg q2w with a loading dose of 600 mg for adolescents (≥12 to <18 years of age) ≥60 kg,

• 200 mg q2w with a loading dose of 400 mg for adolescents (≥12 to <18 years of age) ≥30 kg to <60 kg.

Since the pathogenesis of CSU and response to therapy is thought to be the same in adults and adolescents with CSU (as reflected in identical treatment guidelines), extrapolation from adult efficacy data to adolescents is considered appropriate given the body of knowledge generated for dupilumab across indications.

Population pharmacokinetic analysis of dupilumab using pooled data from Phase 3 studies in patients with Chronic Spontaneous Urticaria (POH0861)

The main objectives of this analysis were:

• To apply the dupilumab global Pop PK base model to patients with CSU.

• To generate individual dupilumab post hoc exposures and assess the influence of intrinsic and extrinsic factors on dupilumab PK in patients with CSU.

Methods

Concentrations of dupilumab in serum and associated dose records from two Phase 3 studies in patients with CSU after SC administration of dupilumab were included in the analysis (EFC16461 Study A and Study B). The analysis was performed with NONMEM (version 7.5.1) running on a LINUX cluster of multi-processor computers.

Considering the PK similarity of dupilumab across different populations, the previously submitted dupilumab global Pop PK base model (POH0668), based on pooled data from HV, patients with AD and asthma, was used in the current analysis for patients with CSU. This global Pop PK model was a two-compartment model with a first order absorption and parallel linear and nonlinear Michaelis-Menten elimination, with body weight as a covariate.

The global Pop PK model was applied to the sparse dupilumab PK data in patients with CSU from the two pivotal Phase 3 studies (EFC16461 Study A and Study B) by fixing all the population parameter estimates to generate individual PK parameters and exposure estimates for patients with CSU using a maximum a posteriori (MAP) Bayesian approach. The agreement between observed dupilumab concentration data and model predicted dupilumab concentrations was confirmed by standard diagnostic criteria, including comparison of model-predicted and observed steady-state exposures, goodness-of-fit plots, quality criteria, and visual predictive checks (VPC).

After confirming the appropriateness of the MAP approach (i.e., external validation of the global Pop PK base model using data from patients with CSU), the global Pop PK base model was used to generate post hoc estimates of individual PK steady-state exposures for each patient with CSU. The influence of selected intrinsic and extrinsic factors on dupilumab PK in patients with CSU was evaluated by comparison of post hoc exposure estimates. The evaluated intrinsic and extrinsic factors in this analysis included demographics (body weight, gender, age, and race), baseline lab parameters (creatinine clearance and albumin), immunogenicity, ethnicity, baseline disease characteristics (ISS7, UAS7, HSS7), CSU patient population (with or without omalizumab treatment), comorbidity (AD) and concomitant medication (H1-antihistamines [H1AH]).

In addition, this validated global Pop PK model was used to simulate dupilumab concentrations over time for regimens of 300 mg q2w (≥60 kg) and 200 mg q2w (30 to <60 kg) in adolescents with CSU, using a virtual adolescent population (12 to <17 years of age, N=926) created from National Health and Nutrition Examination Survey (NHANES). The model simulated exposures at 300 mg q2w and 200 mg q2w in adolescents with CSU were compared with observed/post hoc estimated PK exposure at 300 mg q2w in adult patients with CSU from EFC16461 Study A and Study B; and compared with

previously reported exposures at the approved regimens in adults and adolescents with AD, to demonstrate the similarity of dupilumab exposures across age groups and disease populations (CSU and AD). The typical dupilumab concentrations over time for 300 mg q2w dose regimen in adult patients with AD, asthma, CRSwNP, eosinophilic esophagitis (EoE), prurigo nodularis (PN) and CSU were simulated and compared.

Results

A total of 452 dupilumab concentration records from 124 patients with CSU were available in the Initial Dataset from clinical studies EFC16461 Study A and Study B, after data lock dates. Placebo data were not included in the dataset. Out of 124 patients with CSU, one patient from Study A and two patients from Study B only had one pre-dose dupilumab concentration and were excluded in the PK population (N=121). Within 121 patients, three more patients were excluded, because they had all BLQ data (N=2) or had missed dosing time together with all outlier concentrations (N=1). Three influential concentration data were deemed as significant outliers. Pre-dose (n=116) and post-dose (n=94) samples that were below the lower limit of quantification (BLQ) were flagged in the dataset and excluded from the analysis. In summary, after exclusion of BLQ data and 3 outliers, the Final Dataset contained 239 dupilumab concentrations from 118 patients with CSU (67 patients for EFC16461 Study A and 51 patients for Study B).

There was limited PK data in adolescents and children with CSU in the Final Dataset, with data only available from 3 adolescents and 2 children. Two adolescents with weight ≥60 kg receiving 300 mg q2w both had 2 measurable PK concentrations at Week 12 and 24. The other adolescent with weight 30 to <60 kg receiving 200 mg q2w had 2 measurable PK concentrations at Week 12 and 24. Two children with weight 30 to <60 kg receiving 200 mg q2w discontinued study intervention. No children with weight 15 to <30 kg receiving 300 mg q4w were enrolled.

The characteristics of the 118 patients in the Final Dataset are summarized in Table 2 and Table 3, for potential continuous and categorical covariates, respectively.

Table 2. Descriptive statistics of potential continuous covariates for patients with CSU in the Final Dataset (N=118)

Covariate candidate	EFC16461 Study A and Study B		
	N	Mean (SD)	Median (Min, Max)
Weight (kg)	118	78.7 (19.9)	77 (33, 136)
Age (year)	118	44.0 (16.6)	43 (8, 79)
CLCR for adults (mL/min)[a]	113	143 (45.6)	138 (70, 292)
CLCR for patients <18 years old (mL/min/1.73 m^2)[a]	5	169 (23.5)	176 (137, 191)
Albumin (g/L)	118	45.9 (2.93)	46 (39, 53)
ISS7	118	15.9 (3.95)	16 (8, 21)
UAS7	118	31.2 (7.40)	32 (16, 42)
HSS7	118	15.3 (4.17)	16 (6, 21)

Abbreviation: CLCR: creatinine clearance;, HSS7: weekly hive severity score; ISS7: weekly itch severity score; N: subject number; SD: standard deviation; UAS7: weekly urticaria activity score.

a. For adults, CLCR value was derived using the equation of Cockroft and Gault. For patients <18 years old, CLCR value was derived using the equation of glomerular filtration rate (GFR) Bedside Schwartz.

Table 3. Descriptive statistics of potential categorical covariates for patients with CSU in the Final Data set (N=118)

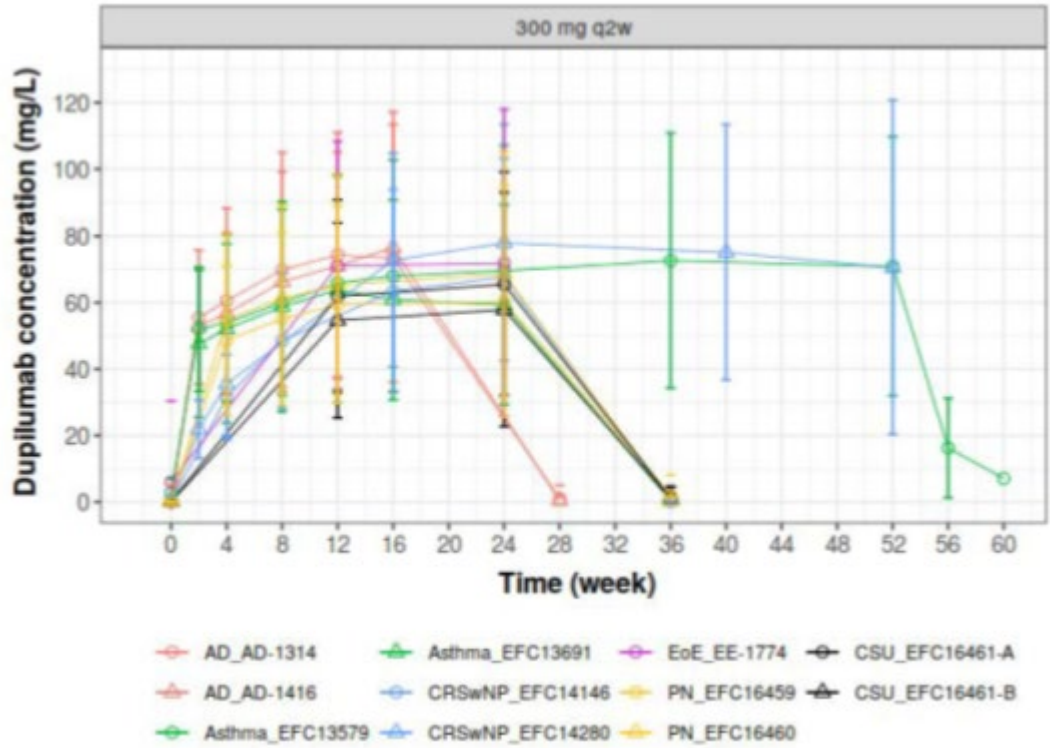
Covariate candidate	Subgroup	EFC16461 Study A and Study B N (%)
Gender	Male	45 (38.1%)
	Female	73 (61.9%)
Race[a]	Caucasian	84 (71.2%)
	Black	4 (3.40%)
	Asian	25 (21.2%)
	Other	3 (2.50%)
	Missing	2 (1.70%)
Stationary ADA	Negative	98 (83.0%)
	Pre-existing	2 (1.70%)
	Treatment-emergent	18 (15.3%)
Stationary ADA	Negative	98 (83.1%)
	Positive	20 (16.9%)
AD	With	6 (5.10%)
	Without	112 (94.9%)
H1AH	Without	2 (1.70%)
	Standard dose	36 (30.5%)
	2-3-fold standard dose	52 (44.1%)
	4-fold standard dose	28 (23.7%)
CSU patient population	CSU patients naive to omalizumab (Study A)	67 (56.8%)
	CSU patients with omalizumab treatment (Study B)	51 (43.2%)

Abbreviation: AD: atopic dermatitis; ADA:anti-drug antibody; CSU: : chronic spontaneous urticaria; H1AH: H1-antihistamines.

[a] One patient from EFC16461 Study A and one patient from EFC16461Study B had missing information for race. In the post hoc analysis, the missing race values were imputed using the categorical value of the majority of the population (i.e., Caucasian).

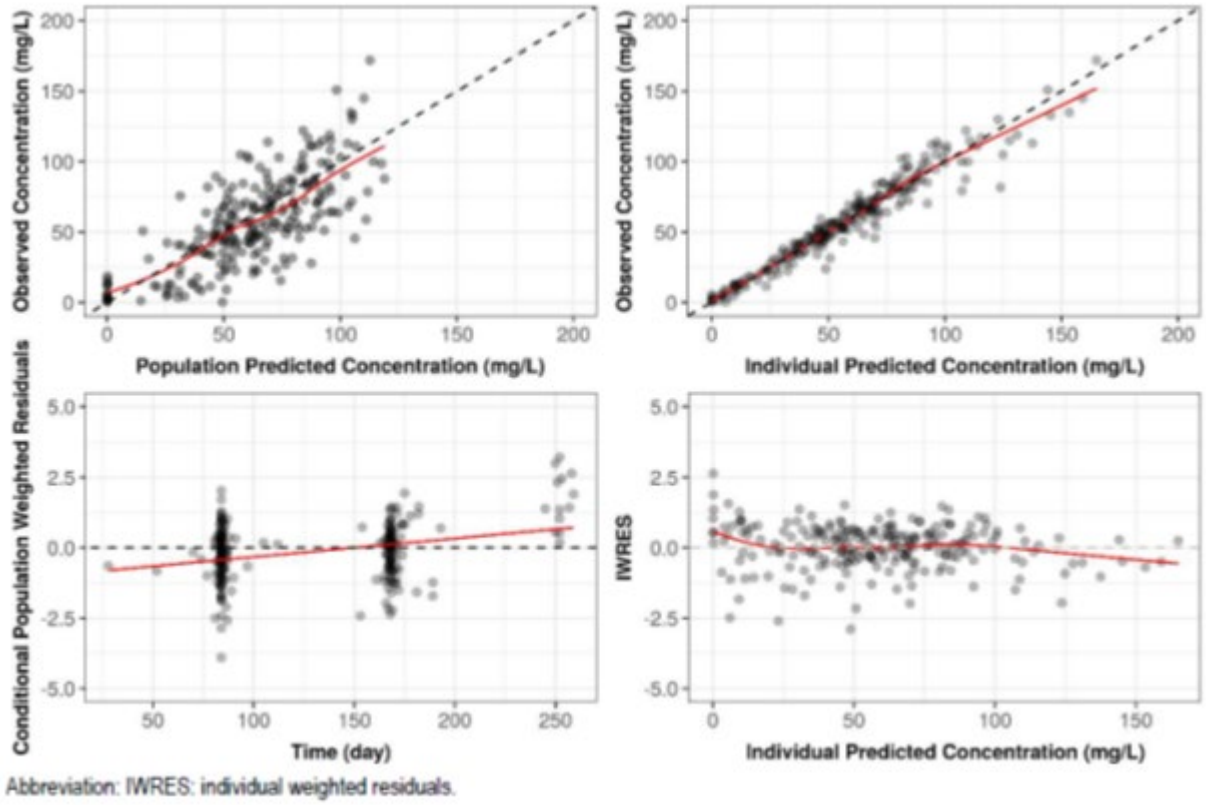
Observed dupilumab PK profiles for patients with CSU, who received 300 mg q2w in studies EFC16461 Study A and Study B were compared to the observed PK profiles for adult AD, asthma, CRSwNP, EoE and PN patients who received 300 mg q2w from 9 Phase 3 studies (AD-1314, AD-1416, EFC13579, EFC13691, EFC14146 and EFC14280, EE-1774, EFC16459 and EFC16460), as shown in Figure 1. The observed mean steady-state trough concentrations were similar across different populations, except for a slower rise of the initial profiles in patients with CRSwNP and EoE, due to the absence of a loading dose. The observed dupilumab steady-state exposures (trough concentrations) were similar across all populations regardless of treatment durations.

Figure 1. Mean (SD) observed trough concentration-time profiles of dupilumab at 300 mg q2w in adult patients with AD, asthma, CRSwNP, EoE, PN and CSU



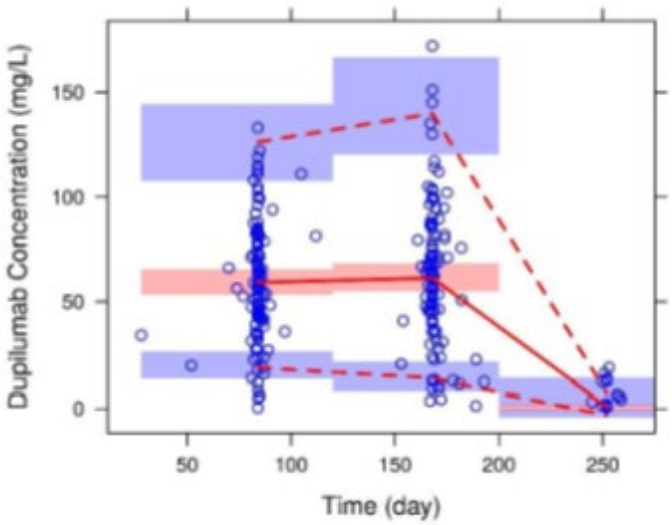
The suitability of the global Pop PK base model to describe dupilumab PK in patients with CSU was evaluated. The relative root mean square error (RMSE) was calculated to be 39.1% for population predicted concentration (PRED). Goodness-of-fit plots (Figure 2) and VPC (Figure 3) all demonstrated a reasonable model performance. These results indicated the adequate predictive performance of the global Pop PK base model in patients with CSU.

Figure 2. Goodness-of-fit plots for applying global Pop PK base model in patients with CSU



Abbreviation: IWRES: individual weighted residuals.

Figure 3. Visual predictive checks for global Pop PK base model in patients with CSU



Legend: blue dots: observations; 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.

Model-based post hoc estimates of dupilumab exposures at steady-state are summarized by study and dose regimen in (Table 4). The mean [SD] predicted trough concentration at steady-state (Ctrough,ss, 63.8 [31.6] mg/L) was similar to the observed Ctrough,ss (61.7 [34.4] mg/L).

Table 4. Mean (SD)[CV%] predicted and observed steady-state exposures of dupilumab in patients with CSU by study and dose regimen in EFC16461 Study A and Study B

Study	Dose regimen[a]	Predicted				Observed	
		N[b] (median weight)	$AUC_{\tau,SS}$[c] (mg•day/L)	$C_{max,SS}$[c] (mg/L)	$C_{trough,SS}$[c] (mg/L)	N[d] (median weight)	$C_{trough,SS}$[e] (mg/L)
EFC16461 Study A	300 mg q2w	61 (75.0 kg)	1130 (479) [42.3%]	89.8 (35.8) [39.9%]	67.1 (31.9) [47.6%]	60 (75.0 kg)	65.5 (33.6) [51.4%]
	200 mg q2w	1 (57.0 kg)	637	52.5	35.3	1 (57.0 kg)	22.4
	All	62 (75.0 kg)	1120 (479) [42.6%]	89.2 (35.8) [40.1%]	66.5 (31.9) [48.0%]	61 (75.0 kg)	64.8 (33.8) [52.2%]
EFC16461 Study B	300 mg q2w	48 (79.5 kg)	1030 (471) [45.9%]	81.8 (34.8) [42.5%]	60.3 (31.2) [51.8%]	47 (79.2 kg)	57.8 (35.1) [60.7%]
Total	300 mg q2w	109 (77.0 kg)	1090 (476) [43.9%]	86.3 (35.4) [41.0%]	64.1 (31.7) [49.4%]	107 (76.0 kg)	62.1 (34.3) [55.3%]
	All	110 (76.5 kg)	1080 (476) [44.0%]	86.0 (35.4) [41.2%]	63.8 (31.6) [49.6%]	108 (75.7 kg)	61.7 (34.4) [55.7%]

Abbreviation: N: number of patients; $AUC_{\tau,ss}$: area under the concentration time curve from time 0 to 14 days at steady state; $C_{max,ss}$: maximum concentration at steady state; $C_{trough,ss}$: minimum concentration at steady state; CV: coefficient of variation; q2w: every two weeks; SD: standard deviation.

a. 200 mg q2w with an initial loading dose of 400 mg and 300 mg q2w with an initial loading dose of 600 mg.

b. For predicted PK exposures, out of 118 patients as PK population in Final Dataset, 115 patients (112 adults and 2 adolescents) received 300 mg q2w and 3 patients (1 adolescents and 2 children 6 to <12 years of age) received 200 mg q2w. Due to dose discontinuation before Week 22, 6 adult patients receiving 300 mg q2w and 2 children 6 to <12 years of age receiving 200 mg q2w were exclude in this post assessment.

c. $AUC_{\tau,ss}$ = AUC[Week 24 – Week 22] for 200 mg q2w and 300 mg q2w. $C_{max,ss}$ and $C_{trough,ss}$ were calculated over Week 22 and Week 24 for 200 mg q2w and 300 mg q2w in EFC16461 Study A and Study B.

d. For observed PK exposure, out of 118 patients as PK population in Final Dataset, 109 patients with CSU (106 adults and 3 adolescents) had measurable PK concentrations at Week 24 . One measurable PK concentration at Week 24 for an adult patient (last received dose at Week 12) was excluded from Bayesian analysis and post assessment because it was identified as outlier due to CWRES>5.

Observed $C_{trough,ss}$ was summarized based on observed data at Week 24 in Pop PK dataset. For EFC16461 Study A, compared to clinical study report (N=64 with observed concentration at Week 24), three patients due to outlier concentrations at Week 24 (N=2) and all BLQ data (N=1) were excluded from the summary of observed $C_{trough,ss}$ at Week 24 here.

The mean (SD) of model-predicted post hoc steady-state exposures of dupilumab in patients with CSU in EFC16461 Study A and Study B as a function of selected intrinsic/extrinsic factors are provided in Table 5. Among the evaluated factors, only body weight exerted a primary effect explaining variability source in dupilumab PK in patients with CSU. Patients in lower body weight group exhibited higher exposures of dupilumab. The summary of predicted dupilumab steady-state exposures by age and dose regimen were presented in Table 6.

All other tested factors had no apparent effect on dupilumab PK exposure based on available data. Some difference in PK exposure across ADA categories (i.e., lower mean exposures in ADA-positive patients, compared to ADA-negative patients) were observed, which may be due to data limitation (<17% patients with positive ADA). The impact of concomitant medication (H1AH) on dupilumab PK exposure was found to be minimal based on available data. There was not enough data (<6% patients with AD) to evaluate the impact of comorbidity (AD) on dupilumab PK exposure in post-hoc assessment.

Table 5. Mean (SD) predicted steady-state exposures for dupilumab in patients with CSU as a function of intrinsic/extrinsic factors

Tested covariates		N[b] (mean weight)	$AUC_{\tau,ss}$[c] (mg.day/L)	$C_{max,ss}$[c] (mg/L)	$C_{trough,ss}$[c] (mg/L)
All		110 (79.1 kg)	1080 (476)	86.0 (35.4)	63.8 (31.6)
Dose regimen[a]	200 mg q2w	1 (57.0 kg)	637	52.5	35.3
	300 mg q2w	109 (79.3 kg)	1090 (476)	86.3 (35.4)	64.1 (31.7)
Age (year)	12-<18 yr	3 (63.1 kg)	1070 (399)	85.3 (30.5)	62.7 (25.7)
	≥18 yr	107 (79.6 kg)	1080 (479)	86.0 (35.6)	63.9 (31.9)
Weight (kg)	<60 kg	22 (55.6 kg)	1520 (524)	119 (37.8)	92.2 (35.5)
	≥60 kg	88 (85.0 kg)	971 (394)	77.6 (29.5)	56.7 (26.4)
Stationary ADA	Negative ADA	92 (77.4 kg)	1160 (465)	91.6 (34.5)	68.8 (31.0)
	Positive ADA	18 (87.8 kg)	690 (319)	56.9 (24.6)	38.2 (21.0)
Sex	Male	42 (84.5 kg)	1110 (372)	87.7 (27.8)	65.6 (24.8)
	Female	68 (75.8 kg)	1060 (532)	84.9 (39.5)	62.7 (35.3)
Race	White	78 (82.1 kg)	1040 (505)	82.6 (37.4)	61.2 (33.6)
	Black	4 (84.7 kg)	1000 (190)	79.9 (13.8)	58.7 (13.1)
	Asian	25 (66.4 kg)	1250 (401)	99.0 (30.3)	74.1 (27.2)
	Other	3 (99.7 kg)	902 (206)	72.0 (15.4)	52.6 (13.7)
Albumin (g/L)	30 - <40	3 (86.7 kg)	773 (571)	62.8 (41.9)	44.0 (37.9)
	40 - <50	94 (78.4 kg)	1090 (483)	86.6 (36.0)	64.4 (32.2)
	≥ 50	13 (82.7 kg)	1090 (407)	86.6 (30.4)	64.6 (26.8)
Renal function[d]	Normal	97 (81.0 kg)	1050 (451)	83.8 (33.7)	62.0 (29.8)
	Mild renal impairment	13 (65.0 kg)	1290 (611)	102 (44.4)	77.6 (41.6)
AD	With	6 (69.8 kg)	1380 (625)	108 (45.9)	83.4 (42.0)
	Without	104 (79.7 kg)	1060 (464)	84.7 (34.5)	62.7 (30.8)
ISS7	<13	23 (80.2 kg)	1000 (379)	79.9 (28.3)	58.0 (24.7)
	≥13	87 (78.9 kg)	1100 (498)	87.6 (37.0)	65.4 (33.2)
UAS7	<28	29 (79.1 kg)	1090 (535)	86.5 (39.5)	64.2 (35.4)
	≥28	81 (79.1 kg)	1080 (456)	85.8 (34.0)	63.7 (30.4)
HSS7	<13	26 (77.6 kg)	1150 (514)	90.9 (38.0)	68.1 (34.2)
	≥13	84 (79.6 kg)	1060 (464)	84.4 (34.6)	62.5 (30.9)
H1AH	without	1 (97.1 kg)	404	39.4	23.3
	standard dose	34 (76.5 kg)	1160 (550)	92.1 (41.1)	69.4 (36.8)
	2-3 fold standard dose	48 (80.3 kg)	1020 (429)	81.7 (31.9)	59.9 (28.6)
	4 fold standard dose	27 (79.7 kg)	1110 (446)	87.5 (33.0)	65.3 (29.4)
Patient Population	CSU patients naive to omalizumab (Study A)	62 (78.1 kg)	1120 (479)	89.2 (35.8)	66.5 (31.9)
	CSU patients with omalizumab treatment (Study B)	48 (80.5 kg)	1030 (471)	81.8 (34.8)	60.3 (31.2)
Ethnicity	Japanese	12 (62.8 kg)	1170 (424)	93.3 (31.6)	68.4 (27.7)
	Non-Japanese	98 (81.1 kg)	1070 (482)	85.1 (35.9)	63.3 (32.2)
	Chinese	11 (71.5 kg)	1290 (411)	102 (31.6)	77.7 (28.8)
	Non-Chinese	99 (80.0 kg)	1060 (479)	84.2 (35.5)	62.3 (31.7)

Abbreviation: AD: atopic dermatitis; ADA: anti-drug antibody; $AUC_{\tau,ss}$: area under the concentration time curve from time 0 to 14 days at steady state; CLCR: creatinine clearance; $C_{max,ss}$: maximum concentration at steady state; $C_{trough,ss}$: minimum concentration at steady state; CSU: chronic spontaneous urticaria ; H1AH: H1-antihistamines; HSS7: weekly hive severity score; ISS7: weekly itch severity score; N: subject number; q2w: every two weeks; SD: standard deviation; UAS7: weekly urticaria activity score.

a. 200 mg q2w with an initial loading dose of 400 mg or 300 mg q2w with an initial loading dose of 600 mg.
b. Out of 118 patients as PK population in Final Dataset, 115 patients received 300 mg q2w and 3 patients received 200 mg q2w. Due to dose discontinuation before Week 22, 6 patients receiving 300 mg q2w and 2 patients receiving 200 mg q2w were exclude in this post assessment.
c. $AUC_{\tau,ss}$ = AUC[Week 24 – Week 22] for 200 mg q2w and 300 mg q2w. $C_{max,ss}$ and $C_{trough,ss}$ were calculated over Week 22 and Week 24 for 200 mg q2w and 300 mg q2w in EFC16461 Study A and Study B.
d. For adults, CLCR value (mL/min) was derived using the euqation of Cockroft and Gault and renal function categories were based on the following creteria: Normal: CLCR ≥ 90 mL/min; Mild renal impairment: 60 ≤ CLCR < 90 mL/min; Moderate renal impairment: 30≤CLCR < 60 mL/min. For adolescents, CLCR value (mL/min/1.73 m^2) was derived using the equation of GFR Bedside Schwartz and same renal function catogories were used: Normal: CLCR ≥ 90 mL/min/1.73 m^2; Mild renal impairment: 60 ≤ CLCR < 90 mL/min/1.73 m^2; Moderate renal impairment: 30≤CLCR < 60 mL/min/1.73 m^2.

Table 6. Mean (SC) [CV%] predicted steady-state exposures of dupilumab in patients with CSU by age and dose regimen in EFC16461 Study A and Study B

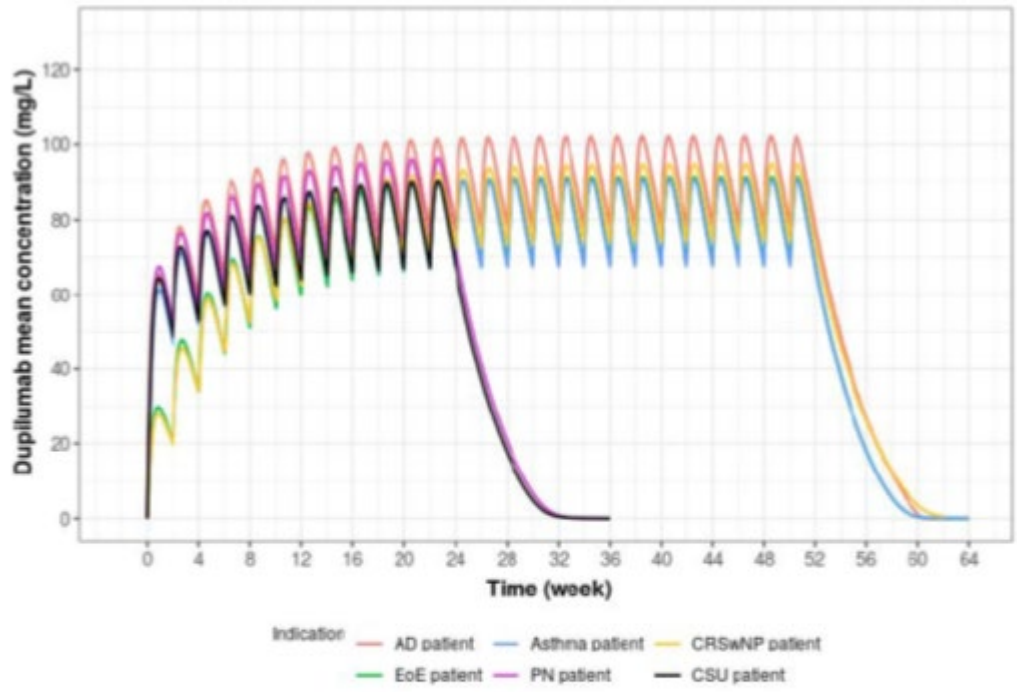
Category		Dose regimen[a]	Predicted N[b] (median weight)	Predicted $AUC_{\tau,ss}$[c] (mg•day/L)	Predicted $C_{max,ss}$[c] (mg/L)	Predicted $C_{trough,ss}$[c] (mg/L)
Age	Adults	300 mg q2w	107 (77.1 kg)	1080 (479) [44.3%]	86.0 (35.6) [41.4%]	63.9 (31.9) [49.9%]
	Adolescents	300 mg q2w	2 (66.1 kg[d])	1280	102	76.4
		200 mg q2w	1 (57.0 kg)	637	52.5	35.3

Abbreviation: N: number of patients; $AUC_{\tau,ss}$: area under the concentration time curve from time 0 to 14 days at steady state; $C_{max,ss}$: maximum concentration at steady state; $C_{trough,ss}$: minimum concentration at steady state; CV: coefficient of variation; q2w: every two weeks; SD: standard deviation.

a. 200 mg q2w with an initial loading dose of 400 mg and 300 mg q2w with an initial loading dose of 600 mg.
b. Out of 118 patients as PK population in Final Dataset, 115 patients received 300 mg q2w and 3 patients received 200 mg q2w. Due to dose discontinuation before Week 22, 6 patients receiving 300 mg q2w and 2 patients receiving 200 mg q2w were exclude in this post assessment.
c. Predicted AUCτ,ss = AUC[Week 24 – Week 22] for 200 mg q2w and 300 mg q2w. Cmax,ss and Ctrough,ss were calculated over Week 22 and Week 24 for 200 mg q2w and 300 mg q2w in EFC16461 study A.
d. Individual body weights for these two adolescent patients with weight ≥60 kg are 60.2 kg and 72.0 kg.

The concentration-time profile of dupilumab in a typical adult patient with CSU (median weight of 77 kg) was simulated at 300 mg q2w (with a loading dose of 600 mg). This typical profile in adult patients with CSU was compared with those in adult patients with AD, asthma, CRSwNP, EoE and PN predicted from the respective Pop PK models. As shown in Figure 4, dupilumab typical concentration-over-time profiles in adult patients with CSU, AD, asthma, CRSwNP, EoE and PN were comparable, which supports the similarity of dupilumab PK across different disease populations. The median time to steady-state was about 10 weeks for 300 mg q2w in a typical patient with CSU. After the last SC dose at steady-state, the model-predicted median time for concentrations to decline to BLQ (0.078 mg/L) was about 12 weeks for 300 mg q2w in a typical patient with CSU.

Figure 4. Comparison of dupilumab typical concentration-time profiles at 300 mg q2w in adult patients with AD, asthma, CRSwNP, EoE, PN and CSU as predicted by Pop PK models

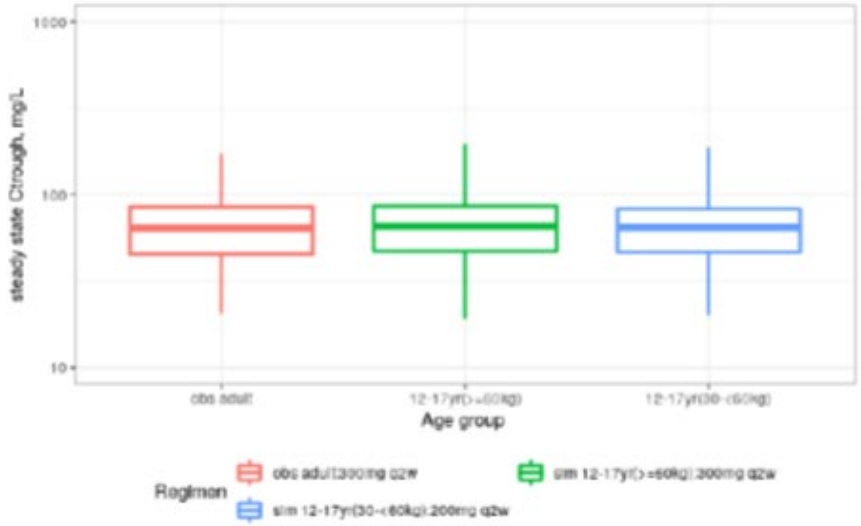


Abbreviations: AD: atopic dermatitis; CSU: Chronic spontaneous urticaria; CRSwNP: chronic rhinosinusitis with nasal polyposis; EoE: Eosinophilic esophagitis; PN: prurigo nodularis.

Note: The typical profile simulation was conducted at 300 mg q2w using Pop PK models of CRSwNP and EoE (without a loading dose), CSU, asthma, AD and PN (with a loading dose) for a typical Caucasian adult with CSU, CRSwNP, asthma, AD, PN or EoE, respectively with demographics described as follows: weight of 75 kg (78 kg for asthma, 73 for PN, 79 kg for CRSwNP, 77 kg for CSU), albumin of 45 g/L, body mass index (BMI) of 25.1 kg/m^2, creatinine clearance normalized to body surface area (CLCRN) of 111 mL/min/1.73 m^2, and eczema area severity index (EASI) of 29.5 (AD only) and negative ADA (median values of the covariates for the respective populations).
Source: POH0861, POH0779, POH0611, POH0530, REGN668-MX-16103-CP-01V1, R668-PK-21229-SR-01V1

The simulated steady-state exposures (Ctrough,ss and Cmax,ss) in adolescents with CSU receiving 200 mg q2w (30 to <60 kg) and 300 mg q2w (≥60 kg) were compared with each other and with the PK exposure the in adult patients with CSU from EFC16461 Study A and Study B, as shown in Figure 5, Figure 6 and Table 7. The simulated steady-state exposure (Cmax.ss and Ctrough.ss) in adolescents 30 to <60 kg receiving 200 mg q2w is comparable to that in adolescents ≥60 kg receiving 300 mg q2w. Also, the simulated steady-state exposure for the 300 mg q2w/200 mg q2w dosing regimens in adolescents is comparable to the observed Ctrough,ss and post hoc estimated Cmax,ss with the 300 mg q2w regimen in adults with CSU.

Figure 5. Boxplot of dupilumab C_{trough} at steady state by age, treatment and body weight groups in patients with CSU

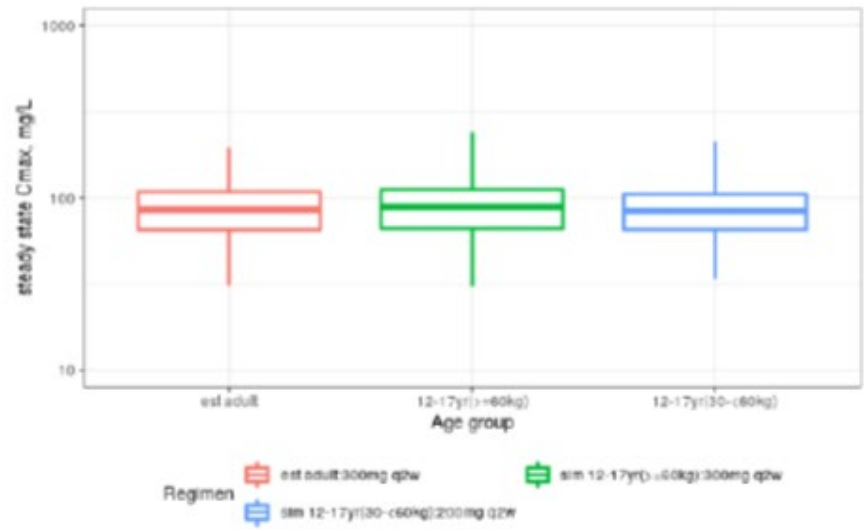


Abbreviation: C_{trough}: trough concentration; NHANES: National Health and Nutrition Examination; obs: observed; q2w: every 2 weeks; q4w: every 4 weeks; sim: simulated.

Source: observed $C_{trough,ss}$ at 300 mg q2w in adults. $C_{trough,ss}$ were simulated at 300 mg q2w and 200 mg q2w in adolescents (≥60 kg) and (30 to <60 kg), respectively, using global Pop PK model based on virtual adolescent population from NHANES.

The upper whisker of the box plot is the largest dataset number smaller than 1.5 interquartile range (IQR) above the third quartile. Similarly, the lower whisker of the box plot is the smallest dataset number larger than 1.5 IQR below the first quartile.

Figure 6. Boxplot of dupilumab C_{max} at steady state by age, treatment and body weight groups in patients with CSU



Abbreviation: C_{max}: maximum concentration; est: estimated using empirical bayesian approach in post hoc assessment; NHANES: National Health and Nutrition Examination; q2w: every 2 weeks; q4w: every 4 weeks; sim: simulated based on Pop PK models based on virtual adolescent population.

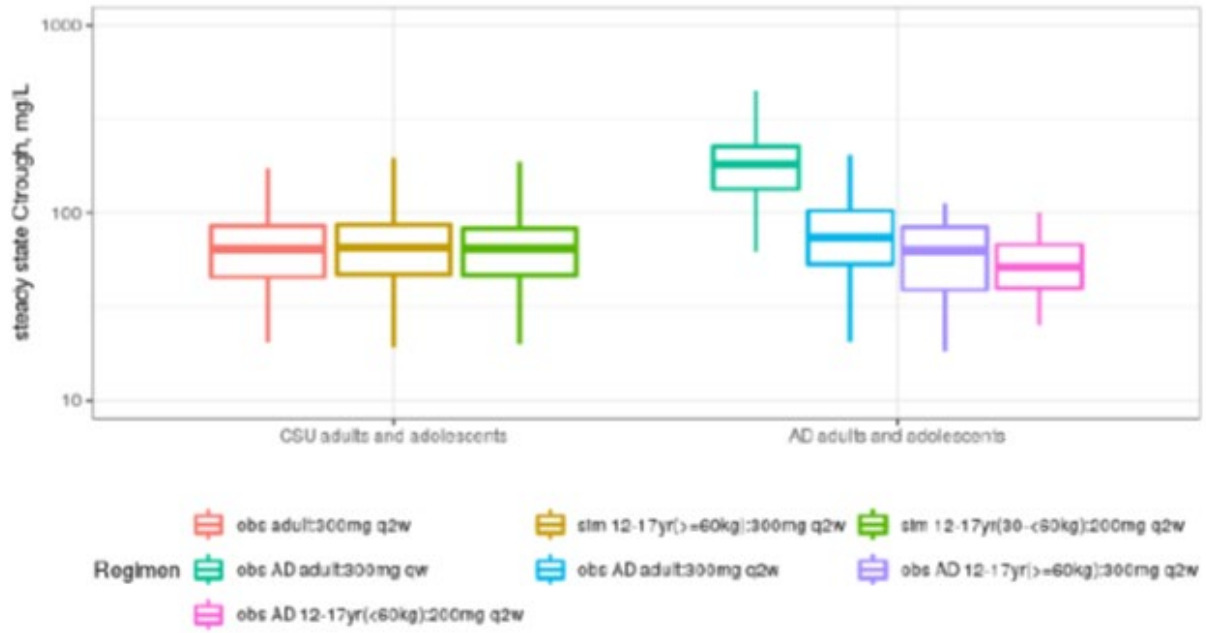
Source: Exposure ($C_{max,ss}$) for CSU adults were from post-hoc estimates of individual PK parameters generated by Pop PK model using empirical bayesian approach in this analysis; Exposure ($C_{max,ss}$) at 300 mg q2w and 200 mg q2w for adolescents (≥60 kg) and (30 to <60 kg), respectively, were simulated using global Pop PK model based on virtual adolescent population from NHANES.

The upper whisker of the box plot is the largest dataset number smaller than 1.5 IQR above the third quartile. Similarly, the lower whisker of the box plot is the smallest dataset number larger than 1.5 IQR below the first quartile.

The PK exposures across disease populations (CSU and AD) were also compared, as shown in Figure 7, Figure 8, and Table 7. The simulated steady-state exposures for the 300 mg q2w/200 mg q2w dosing regimens in adolescents with CSU and the observed/estimated exposure at 300 mg q2w regimen in adults with CSU are comparable to the observed/simulated exposure achieved with the same dose in the corresponding adolescent population with AD, as well as to the exposure achieved with the approved 300 mg q2w regimen in adults with AD.

Overall, the results show that 200 mg q2w (30 to <60 kg) and 300 mg q2w (≥60 kg) in adolescents with CSU would achieve exposure similar to that from 300 mg q2w in adults with CSU and AD, and those from the same dose regimens in adolescents with AD.

Figure 7. Boxplot of dupilumab C_{trough} at steady state by treatment and body weight groups in adults and adolescents with CSU or AD



Abbreviation: C_{trough}: trough concentration; obs: observed; qw: every week; q2w: every 2 weeks; sim: simulated.

Note: Exposure ($C_{trough,ss}$) simulated at 300 mg q2w and 200 mg q2w for adolescents (≥60 kg) and (30 to <60 kg), respectively, using global Pop PK model based on virtual adolescent population from NHANES; observed $C_{trough,ss}$ for all other regimens. Exposures in adults and adolescents with AD were from studies R668-MX-16103-CP-01V1 and R668-PM-18124-SR-01V1, respectively.

The upper whisker of the box plot is the largest dataset number smaller than 1.5 IQR above the third quartile. Similarly, the lower whisker of the box plot is the smallest dataset number larger than 1.5 IQR below the first quartile.

Figure 8. Boxplot of dupilumab C_{max} at steady state by treatment and body weight groups in adults and adolescents with CSU or AD

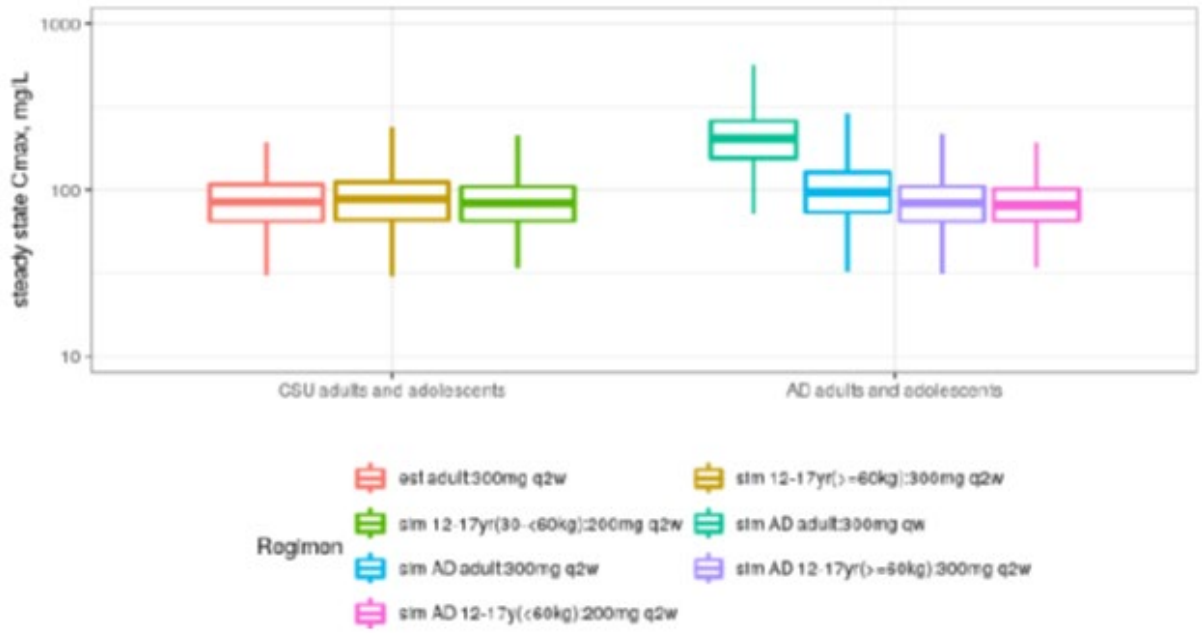
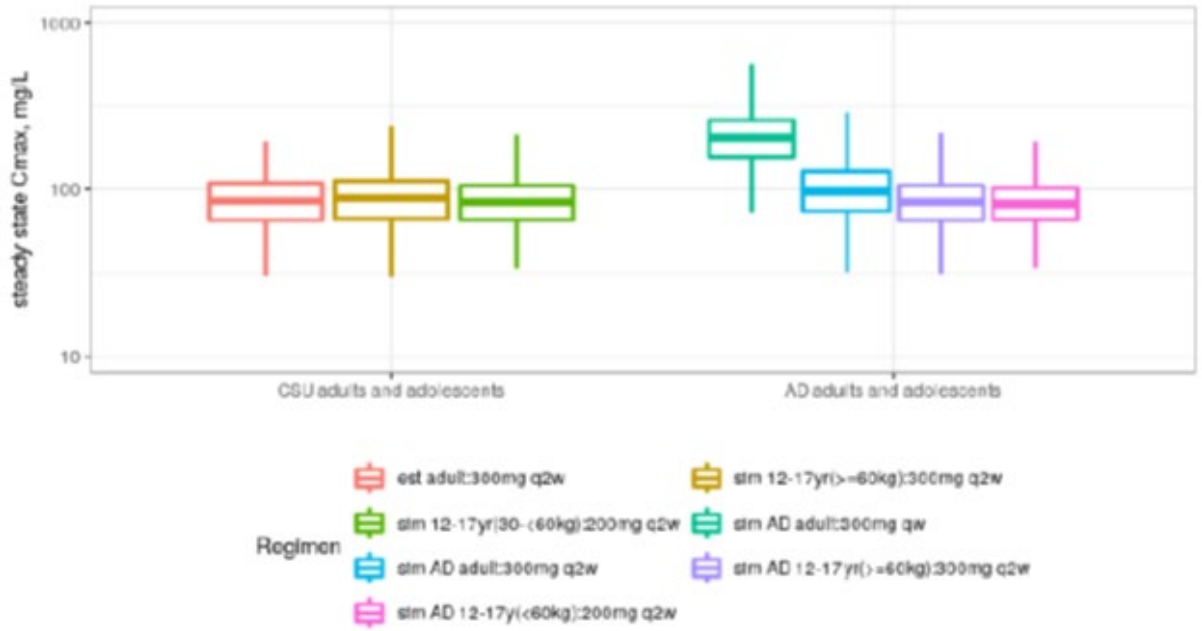


Figure 9. Boxplot of dupilumab Cmax at steady state by treatment and body weight groups in adults and adolescents with CSU or AD



Abbreviation: C_{max}: maximum concentration; est: estimated using empirical bayesian approach in post hoc assessment; qw: every week; q2w: every 2 weeks;; sim: simulated based on Pop PK models based on virtual adolescent population.

Note: Exposure ($C_{max,ss}$) for CSU adults were from post-hoc estimates of individual PK parameters generated by Pop PK model using empirical bayesian approach in this analysis; Exposure ($C_{max,ss}$) at 300 mg q2w and 200 mg q2w for adolescents (≥60 kg) and (30 to <60 kg), respectively, were simulated using global Pop PK model based on virtual adolescent population from NHANES; Exposure ($C_{max,ss}$) of 300 mg q2w and 300 mg qw in adults with AD was simulated from Study R668-PM-19142-SR-01V1; Exposure ($C_{max,ss}$) at 300 mg /200 mg q2w in adolescents with AD was simulated from Study R668-PM-18124-SR-01V1.

The upper whisker of the box plot is the largest dataset number smaller than 1.5 IQR above the third quartile. Similarly, the lower whisker of the box plot is the smallest dataset number larger than 1.5I QR below the first quartile.

Table 7. Model-predicted and observed steady state exposure of dupilumab in patients with CSU and AD

Population	Age group	Study identifier	Dose	Median body weight (kg)	Predicted/Simulated $C_{max,ss}$ (mg/L)[a]			Observed/Simulated $C_{trough,ss}$ (mg/L)[a]		
					N	Mean (SD)	P5-P95	N	Mean (SD)	P5-P95
CSU	Adults	EFC16461 Study A[a]	300 mg q2w	75.1	60	89.4 (36.0)	24.0-153	62	63.5 (34.2)	3.63-117
		EFC16461 Study B[a]	300 mg q2w	80.0	47	81.6 (35.1)	33.7-142	46	57.7 (35.5)	10.4-112
AD	Adults	R668-AD-1334 R668-AD-1416[b]	300 mg qw	75.2	5000	216 (84.3)	108-371	417	183 (77.0)	66.0-325
AD	Adults	R668-AD-1334 R668-AD-1416[b]	300 mg q2w	75.0	5000	105 (43.2)	48.3-186	438	75.0 (40.3)	12.4-141
CSU	Adolescents	POH0861[c]	300 mg q2w (≥60 kg)	73.7	1000	91.2 (35.7)	37.7-154	1000	68.6 (32.2)	22.2-125
			200 mg q2w (30-<60 kg)	51.3	1000	87.6 (31.5)	43.4-144	1000	66.9 (28.1)	28.4-118
AD	Adolescents	R668-AD-1526[b]	300 mg q2w (≥60 kg)	80.3	4140	87.0 (31.8)	41.0-144	36	57.9 (30.0)	13.7-102
			200 mg q2w (<60 kg)	49.0	3860	86.1 (28.8)	49.2-142	41	51.6 (24.0)	10.8-94.3

Abbreviations: C_{max}: maximum concentration at steady state; $C_{trough,ss}$: trough concentration at steady state; N: number of patients; q2w: every 2 weeks; q4w: every 4 weeks; SD: standard deviation, P5: 5th percentile; P95: 95th percentile

a Predicted $C_{max,ss}$ generated from Pop PK model predicted individual post hoc parameters using bayesian approach; observed $C_{trough,ss}$ for adult patients with CSU

b Simulated $C_{max,ss}$; observed $C_{trough,ss}$ for adults and adolescents with AD

c Simulated $C_{trough,ss}$ and $C_{max,ss}$ based on Pop PK model for 300 mg q2w and 200 mg q2w in adolescents with CSU (≥60 kg) and (30 to <60 kg), respectively, using virtual pediatric population from NHANES.

Source: observed $C_{trough,ss}$ and simulated $C_{max,ss}$ in adults and adolescents with CSU (Study POH0861) and observed $C_{trough,ss}$ for adults and adolescents with AD (R668-AD-1334-CP-01V1, R668-AD-1416-CP-01V1, R668-AD-1526-CP-01V2). Simulated $C_{max,ss}$ of 300 mg q2w / 300 mg qw in adults with AD, (Study R668-PM-19142-SR-01V1); Simulated $C_{max,ss}$ 300 mg q2w / 200 mg q2w in adolescents with AD (Study R668-PM-18124-SR-01V1) .

2.3.3. Pharmacodynamics

PD and immunogenicity data were collected in the two Phase 3 studies in patients with CSU (EFC16461 Study A and Study B). The treatment effect of dupilumab on a type 2 biomarker measured in blood (total IgE) over time was evaluated, and comparisons of treatment effect of dupilumab on total IgE with the previously reported analyses in AD, asthma, CRSwNP, EoE and PN patients were described. Exposure-response (E-R) relationships were analysed using descriptive exposure quartile and/or model-based analyses for the efficacy endpoints: urticaria activity score over 7 days (UAS7), itch severity score over 7 days (ISS7), and hives severity score over 7 days (HSS7), at Week 24.

The underlying pathologic mechanism for CSU, while not fully understood, is thought to be related mainly to mast cells and basophil activation, which include IgE mediated and non-IgE mediated mechanisms. To date there is no available validated CSU specific biomarker which can be used for disease activity evaluation nor for treatment effect assessment. Total IgE was evaluated in the CSU development program to better understand and further characterise dupilumab's mode of action in CSU.

Mechanism of action

Dupilumab is a recombinant human immunoglobulin-G4 (IgG4) monoclonal antibody (mAb) that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signalling by specifically binding to the IL-4 receptor alpha (IL-4Rα) subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signalling via the Type 1 receptor (IL-4Rα/γc), and both IL-4 and IL-13 signalling through the Type 2 receptor (IL-4Rα/IL-13Rα). As a dual, selective inhibitor of IL-4 and IL-13 through this pathway, dupilumab inhibits both receptor-mediated activation and the downstream pro-inflammatory signalling, which play critical roles in the pathogenesis of T-helper 2 (TH2) mediated diseases such as AD, asthma, CRSwNP, EoE, PN and CSU).

Primary pharmacology

Total IgE in serum

Blocking of the IL 4Rα receptor subunit with dupilumab inhibits IL 4 and IL 13 (type 2) cytokine-induced responses, including the release of pro-inflammatory cytokines, chemokines, and IgE through this pathway. Total IgE in serum was assessed in patients with CSU in EFC16461 Study A and Study B. In Study A, dupilumab was to be administered at doses defined by age and weight for adults, adolescents (≥12 to <18 years), and children (≥6 to <12 years in some selected countries) q2w or q4w. In Study B, dupilumab was administered at doses defined by age and weight for adults and adolescents (≥12 to <18 years) q2w. In both Study A and Study B, blood samples for measurement of total IgE in serum were collected at the time points (baseline, on-treatment at Week 12 and Week 24 and follow up at Week 36).

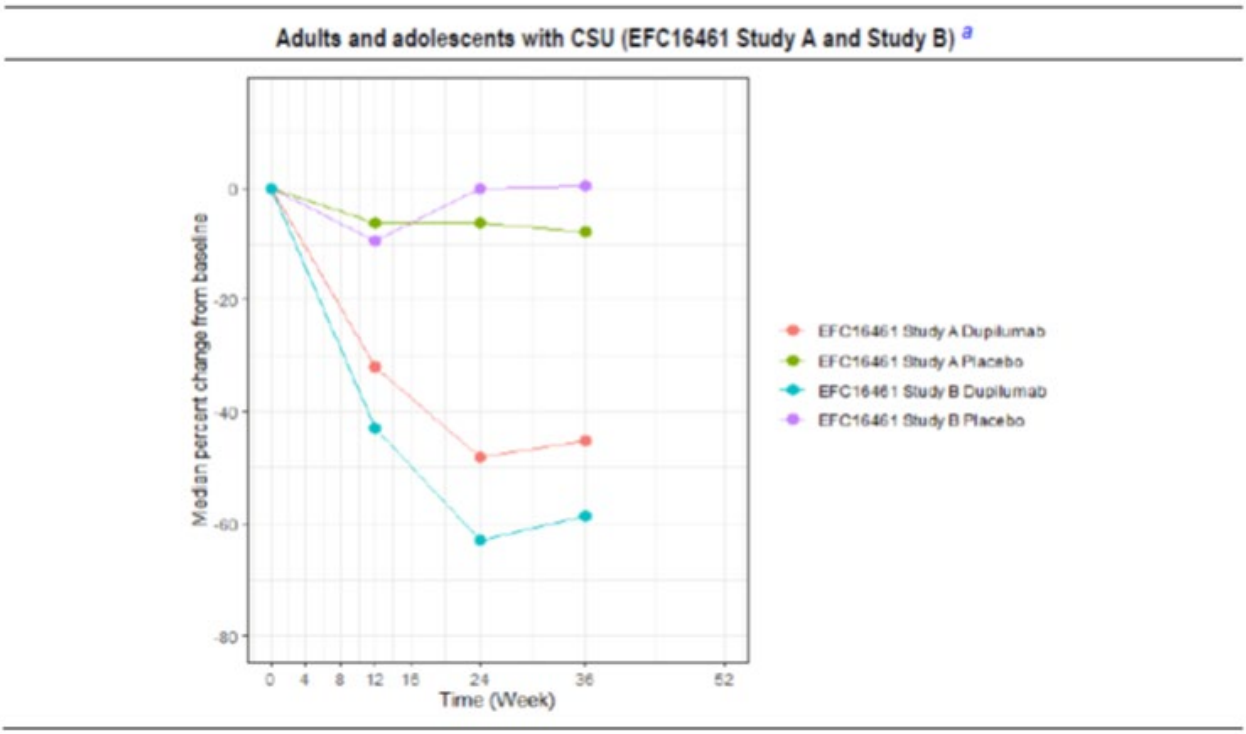
Results

Concentrations of total IgE in serum showed a continuous decline throughout the dupilumab treatment period, in contrast to the absence of notable effects in patients who received placebo. Median total IgE concentrations at baseline were 109 IU/mL and 72.1 IU/mL for the dupilumab group and 96.5 IU/mL and 85.8 IU/mL for the placebo group in EFC16461 Study A and Study B, respectively. There was no meaningful difference in median percent reduction from baseline in total IgE concentrations between Study A and Study B: 48.2% and 63.0% for the dupilumab group at Week 24, and 45.2% and 58.6% at follow-up Week 36 (post treatment), in EFC16461 Study A and Study B, respectively. The specific

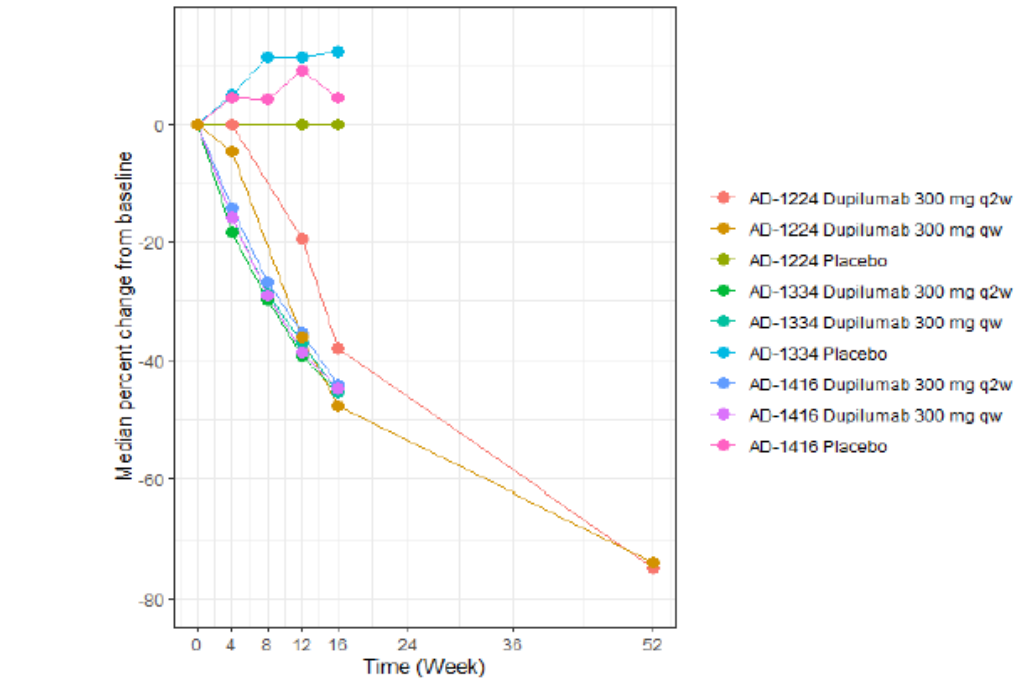
decline in total IgE indicated that type 2 mediated immunoglobulin class switching to the allergic phenotype (ie, IgM to IgE) was effectively blocked by dupilumab treatment. The total IgE profiles showed a similar median magnitude of effect over time in CSU, AD, asthma, CRSwNP, EoE and PN patient populations (Figure 10).

Concentrations of total IgE in serum in adolescents and 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. In Study A, 1 adolescent (who received dupilumab 300 mg q2w) had an IgE concentration at Week 24 that showed a 62.2% decrease from baseline; the other adolescent who received dupilumab (200 mg q2w) had no baseline serum IgE for comparison. The other two adolescents received placebo, one of whom had a total serum IgE decrease of approximately 44% at Week 24, while the other had total IgE in serum decrease of approximately 25% at Week 13 (early discontinuation). Two children with body weight ≥30 kg to <60 kg who received dupilumab 200 mg q2w discontinued study intervention early (one at Week 10 and the other at Week 4). Both showed a decrease from baseline in total IgE in serum concentrations (16.1% at Week 13 and 23.7% at Week 7, respectively. In Study B, the 1 adolescent participant who received dupilumab 300 mg q2w had an IgE concentration at Week 24, with a 70.8% decrease from baseline in total IgE in serum.

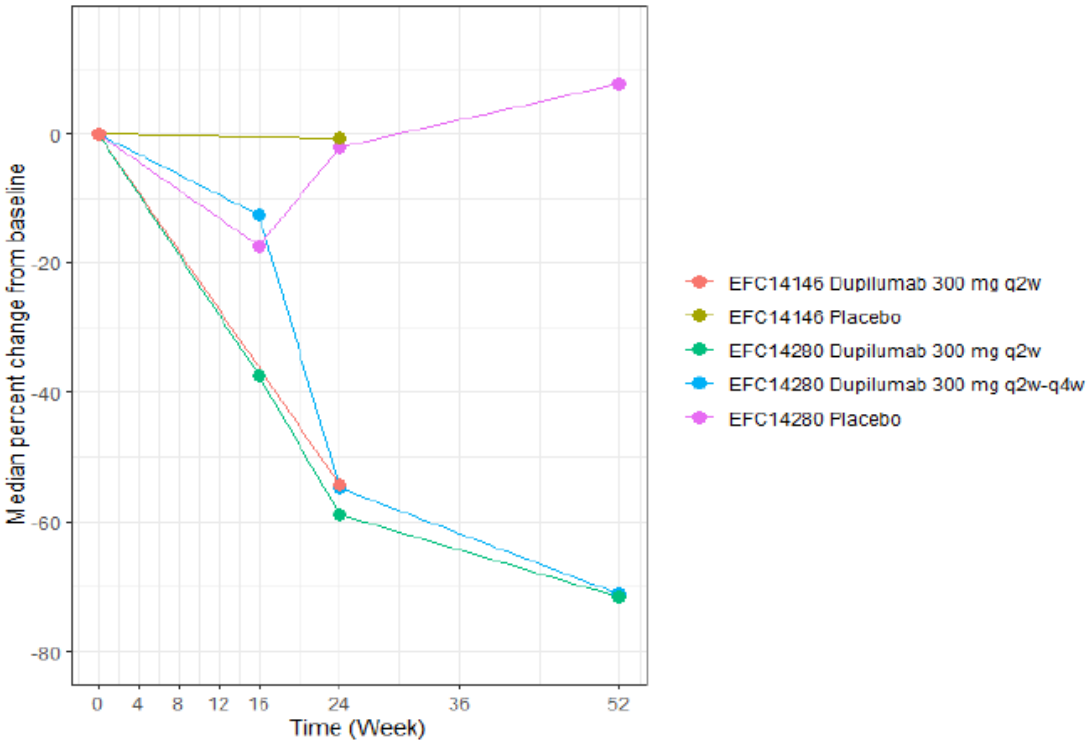
Figure 10. Median percent change in total IgE in serum over time following dupilumab or placebo in adults and adolescents with CSU, adults with AD, adults with CRSwNP, adults with PN, adolescents and adults with asthma, and adolescents and adults with EoE



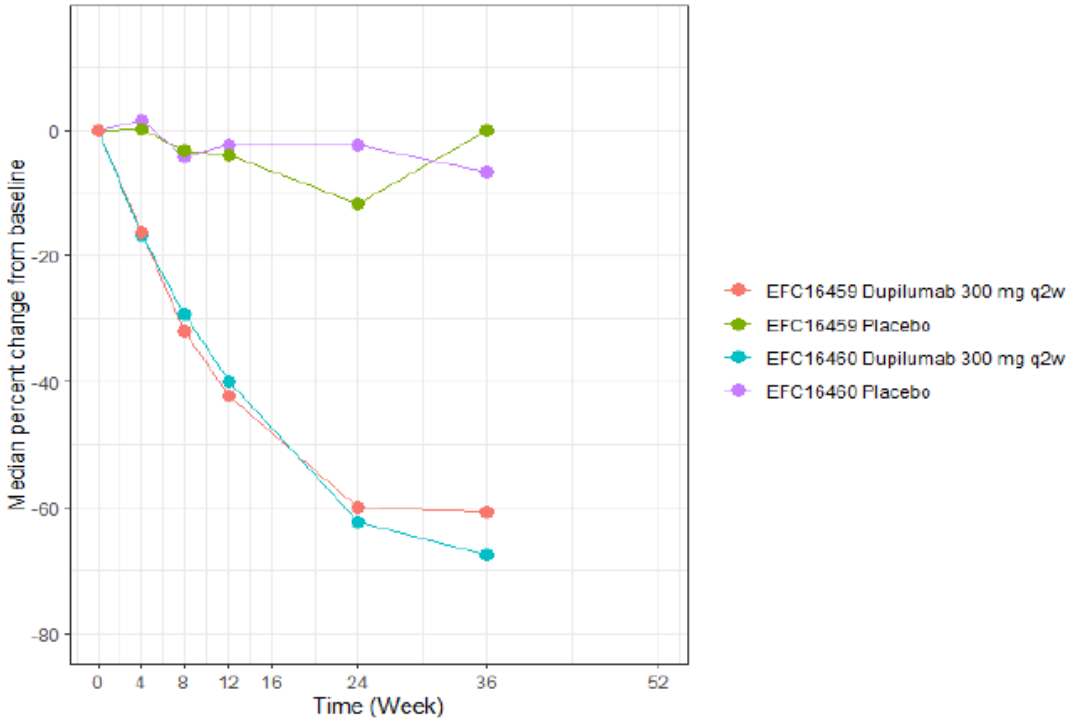
Adults with AD (Studies R668-AD-1224 [b], R668-AD-1334[c] and R668-AD-1416[d])



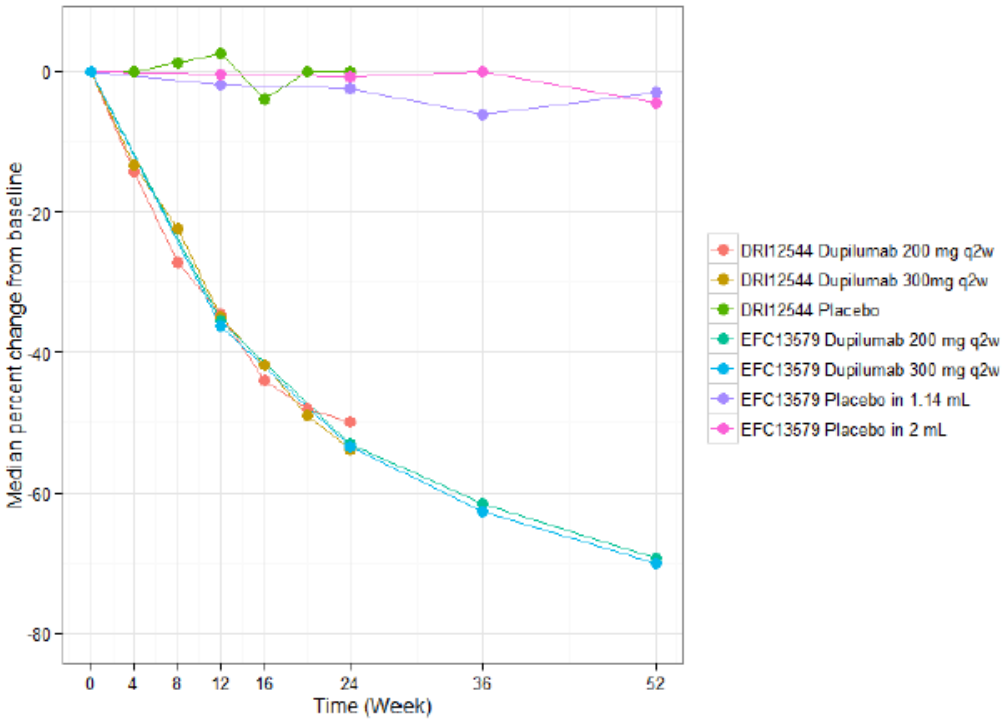
Adults with CRSwNP (Studies EFC14146[e] and EFC14280[f])



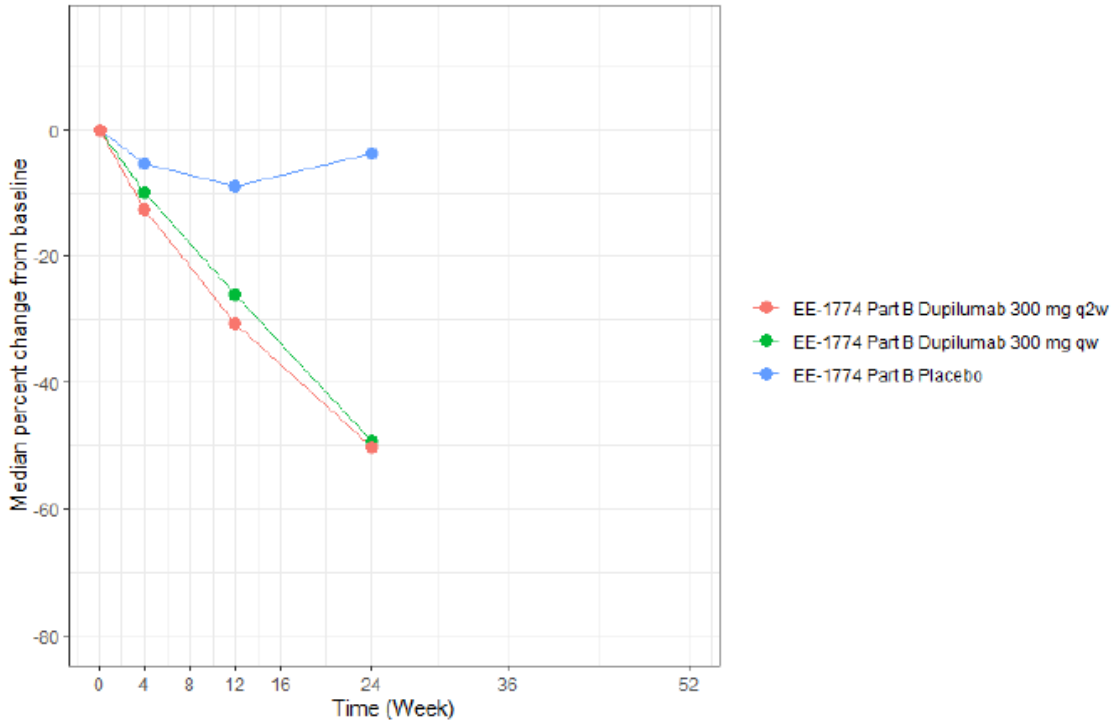
Adults with PN (Studies EFC16459 and EFC16460)[g]



Adults and adolescents with asthma (Studies DRI12544[h] and EFC13579[i])



Adults and adolescents with EoE (Study R668-EE-1774 Part B)[j]



Abbreviations: EOS, end of study; EOT, end of treatment.

a EFC16461 Study A dupilumab N = 66, placebo N = 65. EOT = 24 weeks; EOS = 36 weeks. EFC16461 Study B dupilumab N = 52, placebo N = 52. EOT = 24 weeks; EOS = 36 weeks.

b R668-AD-1224 300 mg q2w N = 89, 300 mg qw N =270, placebo N = 264. EOT = 52 weeks.

c R668-AD-1334 300 mg q2w N = 224, 300 mg qw N =223, placebo N = 224. EOT = 16 weeks; EOS = 28 weeks.

d R668-AD-1416 300 mg q2w N =233, 300 mg qw N =239, placebo N = 236. EOT = 16 weeks; EOS = 28 weeks.

e EFC14146 300 mg q2w N =143, placebo N = 132. EOT = 24 weeks; EOS = 48 weeks.

f EFC14280 300 mg q2w N =148, 300 mg q2w-q4w N =148, placebo N = 150. EOT = 52 weeks; EOS = 64 weeks.

g EFC16459 dupilumab N = 74, placebo N = 73. EOT = 24 weeks; EOS = 36 weeks; EFC16460 dupilumab N = 76, placebo N = 79. EOT = 24 weeks; EOS = 36 weeks

h DRI12544 200 mg q2w N = 148, 300 mg q2w N = 156, placebo N = 158. EOT = 24 weeks; EOS = 40 weeks.

i EFC13579 200 mg q2w N = 629, 300 mg q2w N = 632, placebo 1.14 mL (matching placebo for 200 mg q2w) N = 315, placebo 2 mL (matching placebo for 300 mg q2w) N = 321. EOT = 52 weeks; EOS = 64 weeks.

j R668-EE-1774 Part B dupilumab 300 mg q2w=81, dupilumab 300 mg qw=80, placebo N =79

The Figure shows the on-treatment data for AD, CRSwNP, Asthma and EoE, and including the off-treatment data (at Week 36) for CSU and PN

Source: 5.3.5.1 (Study EFC16461 Study A and Study B of the current submission); 5.3.5.1 R668-AD-1224, 5.3.5.1 (R668-AD-1334) and 5.3.5.1 (R668-AD-1416), previously submitted in the applications for adults and adolescents with AD; 5.3.5.1 (Study EFC14146) and 5.3.5.1 (EFC14280), previously submitted in the marketing application for adults with CRSwNP; 5.3.5.1 (Studies EFC16459 and EFC16460), previously submitted in the marketing application for adults with PN; 5.3.5.1 (Study R668-EE-1774 Part B), previously submitted in the marketing application for adults and adolescents with EoE; 5.3.5.1 (Study DRI12544) and 5.3.5.1 (Study EFC13579), previously submitted in the marketing application for adults and adolescents with asthma.

Immunogenicity

Immunogenicity was assessed in patients with CSU in EFC16461 Study A and Study B. In both studies, blood samples for detection of ADA in serum were collected at the time points (baseline, on-treatment at Week 12 and Week 24 and follow up at Week 36). The pool of dupilumab arms over 36 weeks (24 weeks on-treatment and 12 weeks follow up) in EFC16461 Study A and Study B was the source of data to evaluate ADA responses in patients with CSU.

The incidence of treatment-emergent ADAs through Week 36 was 15.7% in the dupilumab group compared to 2.5% in the placebo group (Table 8). Persistent ADA responses were observed in 6.6% of

patients receiving dupilumab compared to 0% for placebo. Of the 19 patients with treatment-emergent ADA in the dupilumab group, 17 had low titer and only 2 had moderate-titer responses. High titer ADA response (>10 000) was not observed. A total of 13.2% of patients receiving dupilumab were classified as NAb-positive compared to 1.7% of patients in the placebo group (Table 8). The ADA responses in patients with CSU who are intolerant or incomplete responders to omalizumab in Study B are similar to Study A (Table 8).

Table 8. ADA incidence in Phase 3 studies in patients with CSU (EFC16461 Study B and Study A) through Week 36 (on-treatment period and follow up period)

Anti-dupilumab antibodies N (%)	EFC16461 Study A		EFC16461 Study B		Pool (Study A and Study B)	
	Placebo (N=66)	Dupilumab[a] (N=69)	Placebo (N=53)	Dupilumab[a] (N=52)	Placebo (N=119)	Dupilumab[a] (N=121)
Pre-existing ADA[b]	0 (0%)	1 (1.4%)	1 (1.9%)	1 (1.9%)	1 (0.8%)	2 (1.7%)
Treatment-emergent response[c]	1 (1.5%)	9 (13.0%)	2 (3.8%)	10 (19.2%)	3 (2.5%)	19 (15.7%)
Persistent response[d]	0 (0%)	3 (4.3%)	0 (0%)	5 (9.6%)	0 (0%)	8 (6.6%)
Indeterminate response[e]	0 (0%)	5 (7.2%)	0 (0%)	5 (9.6%)	0 (0%)	10 (8.3%)
Transient response[f]	1 (1.5%)	1 (1.4%)	2 (3.8%)	0 (0%)	3 (2.5%)	1 (0.8%)
Peak post-baseline titer						
Low (<1,000)	1 (1.5%)	9 (13.0%)	2 (3.8%)	8 (15.4%)	3 (2.5)	17 (14.0%)
Moderate (1,000-10,000)	0 (0%)	0 (0%)	0 (0%)	2 (3.8%)	0 (0%)	2 (1.7%)
High (>10,000)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Treatment-boosted response[g]	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Neutralizing antibodies	0 (0%)	8 (11.6%)	2 (3.8%)	8 (15.4%)	2 (1.7%)	16 (13.2%)

a Dupilumab dosing regimen: including both 300 mg q2w and 200 mg q2w regimens (see Table 1).
b Either an ADA-positive response in the ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline in the ADA assay with all post first dose ADA results less than 4-fold over baseline titer levels.
c A positive response in the ADA assay post first dose when baseline results are negative or missing.
d Treatment emergent ADA-positive response with two or more consecutive ADA-positive sampling time points separated by greater than 12-week period (greater than 84 days), with no ADA negative samples in between.
e Treatment-emergent response with only the last collected sample positive in the ADA assay.
f Treatment-emergent ADA-positive response that is not considered persistent or indeterminate.
g A positive response in the ADA assay post first dose that is greater than or equal to 4-fold over baseline titer levels, when baseline results are positive.

Source: 5.3.5.1 Studies EFC16461 Study A and Study B, Appendix 16.2.5 Compliance and drug concentration data [16.2.5.4.2.2.6] and [16.2.5.4.2.2.8]; 5.3.5.3 ISS Appendix 7 [7.2.1]

The treatment-emergent ADA incidence through Week 24 (on-treatment period) was 6.6% in the dupilumab group compared to 0.8% in the placebo group (Table 9). Persistent ADA responses were observed in 0.8% of patients receiving dupilumab compared to 0% for placebo. Of the 8 patients with treatment-emergent ADA in the dupilumab group, 7 had low titer and only 1 had moderate titer responses. High titer ADA response (>10 000) was not observed. A total of 1.7% of patients receiving dupilumab were classified as NAb-positive compared to 0.8% of patients in the placebo group (Table 9). The ADA responses in on-treatment period in patients with CSU who are intolerant or incomplete responders to omalizumab in Study B are similar to Study A.

Table 9. ADA incidence in Phase 3 studies in patients with CSU (EFC16461 Study B and Study A) through Week 24 (on-treatment period)

Anti-dupilumab antibodies N (%)	EFC16461 Study A		EFC16461 Study B		Pool (Study A and Study B)	
	Placebo (N=66)	Dupilumab[a] (N=69)	Placebo (N=53)	Dupilumab[a] (N=52)	Placebo (N=119)	Dupilumab[a] (N=121)
Pre-existing ADA[b]	0 (0%)	1 (1.4%)	1 (1.9%)	1 (1.9%)	1 (0.8%)	2 (1.7%)
Treatment-emergent response[c]	0 (0%)	4 (5.8%)	1 (1.9%)	4 (7.7%)	1 (0.8%)	8 (6.6%)
Persistent response[d]	0 (0%)	0 (0%)	0 (0%)	1 (1.9%)	0 (0%)	1 (0.8%)
Indeterminate response[e]	0 (0%)	2 (2.9%)	1 (1.9%)	2 (3.8%)	1 (0.8%)	4 (3.3%)
Transient response[f]	0 (0%)	2 (2.9%)	0 (0%)	1 (1.9%)	0 (0%)	3 (2.5%)
Peak post-baseline titer						
Low (<1,000)	0 (0%)	4 (5.8%)	1 (1.9%)	3 (5.8%)	1 (0.8%)	7 (5.8%)
Moderate (1,000-10,000)	0 (0%)	0 (0%)	0 (0%)	1 (1.9%)	0 (0%)	1 (0.8%)
High (>10,000)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Treatment-boosted response[g]	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Neutralizing antibodies	0 (0%)	1 (1.4%)	1 (1.9%)	1 (1.9%)	1 (0.8%)	2 (1.7%)

a Dupilumab dosing regimen: including both 300 mg q2w and 200 mg q2w regimens (see Table 1).

b Either an ADA-positive response in the ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline in the ADA assay with all post first dose ADA results less than 4-fold baseline titer levels.

c A positive response in the ADA assay post first dose when baseline results are negative or missing.

d Treatment emergent ADA-positive response with two or more consecutive ADA-positive sampling time points separated by greater than 12-week period (greater than 84 days), with no ADA negative samples in between.

e Treatment-emergent response with only the last collected sample positive in the ADA assay.

f Treatment-emergent ADA-positive response that is not considered persistent or indeterminate.

g A positive response in the ADA assay post first dose that is greater than or equal to 4-fold over baseline titer levels, when baseline results are positive.

Source:PGM=PRODOPS/SAR231893/EFC16461/CSR_A3/EXPLO/PGM/a_pk_sum_ada_cat_a_t.sas OUT=EXPLO/OUTPUT/a_pk_sum_ada_cat_a_t_j.rtf (27OCT2022 3:52)
PGM=PRODOPS/SAR231893/EFC16461/CSR_B4/EXPLO/PGM/a_pk_sum_ada_cat_a_t.sas OUT=EXPLO/OUTPUT/a_pk_sum_ada_cat_a_t_j.rtf (27OCT2022 3:51)
PGM=PRODOPS/SAR231893/OVERALL/ISS_CSU_2021/EXPLO/PGM/a_pk_sum_ada_cat_a_t.sas OUT=EXPLO/OUTPUT/a_pk_sum_ada_cat_a_t_j.rtf (26OCT2022 11:20)

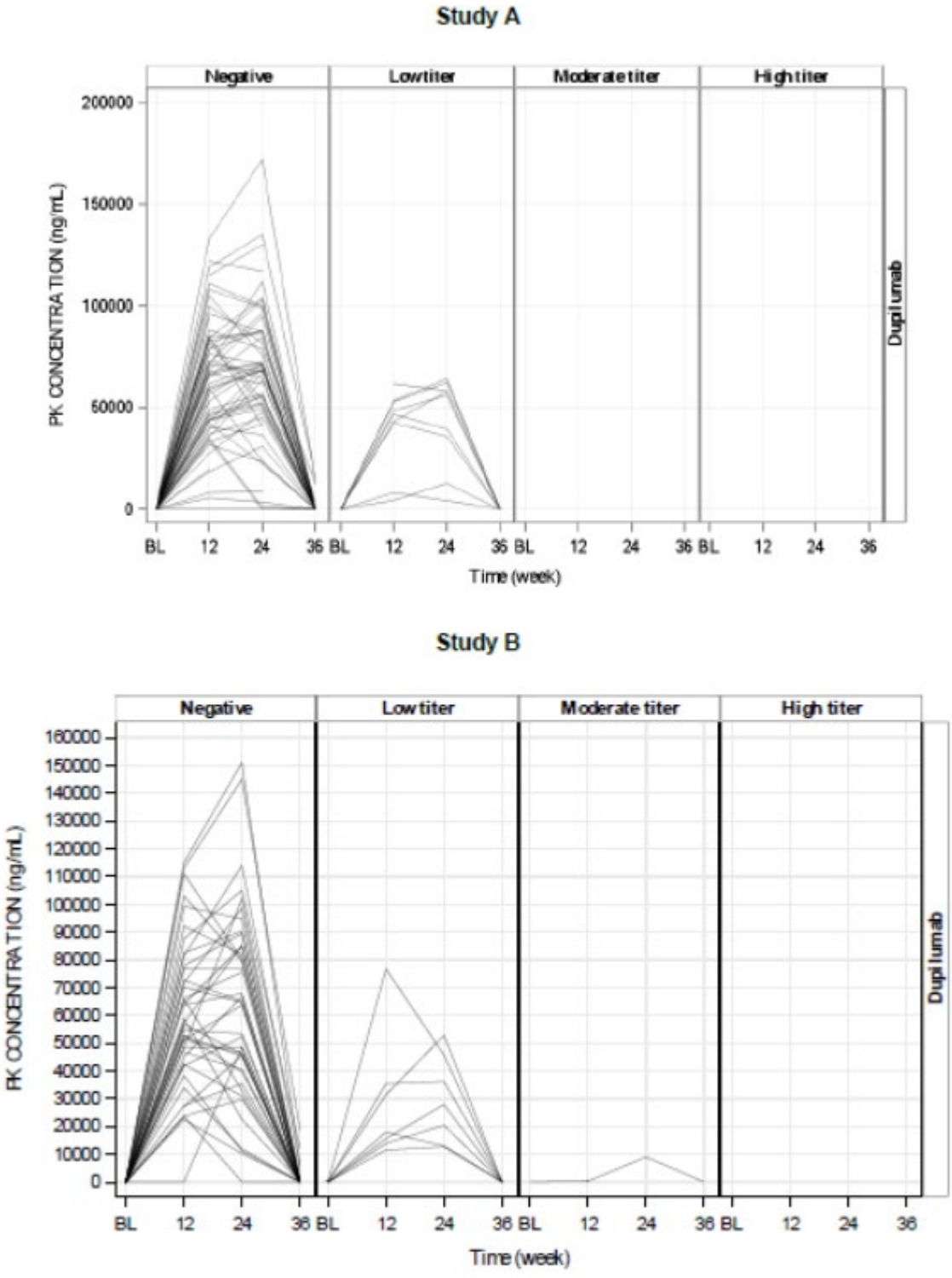
Following dupilumab treatment for 24 weeks the proportion of patients with a treatment-emergent ADA positive response during the on-treatment period was similar at Week 12 and Week 24 (6.6% to 7.1%). However, the proportion of patients with a treatment-emergent ADA positive response in the post-treatment period increased to 15.7%. High systemic concentrations of protein therapeutics are known to be tolerogenic and, conversely, lower exposure to an antigen can potentially stimulate immune responses. Therefore, the development of low titer ADAs in a small number of patients at Week 36 may be associated with a lower drug exposure after cessation of drug treatment.

The ADA and NAb incidences in patients with CSU, AD, asthma, CRSwNP, EoE, and PN are provided. The ADA and NAb incidences are summarized for the on-treatment period in patients with CSU, AD, asthma, EoE and mainly the on-treatment period in patients with CRSwNP and PN (with limited number of patients with 12 weeks follow-up period). Notwithstanding the limitations associated with comparing the immunogenicity of dupilumab across different populations, the ADA incidence was generally similar across the AD, asthma, CRSwNP, EoE, PN and CSU populations in the on-treatment period with respect to treatment-emergent positive ADA response (2.6-7.7%), persistent ADA

response (0-2.1%), and NAb response (1.0-3.4%) after 24 or 52 weeks of treatment with dupilumab 300 mg Q2W with or without a loading dose.

The individual concentrations observed in study participants with low-titer ADA response were generally within the concentration range in ADA-negative study participants (EFC16461 Study B and Study A) (Figure 11). There was no clear evidence of lack or loss of efficacy in 17 study participants who developed ADA (including NAb) response with low titer. The safety profile in study participants with a positive ADA status appeared similar to that of study participants with a negative ADA status.

Figure 11. Individual concentration-time profiles of dupilumab by ADA titer category through Week 36 (on-treatment period and follow up period) in EFC16461 in patients with CSU



Source: EFC16461 Study A and Study B, Appendix 16.2.5 Compliance and drug concentration data [16.2.5.4.2.1.5].

2.3.4. PK/PD modelling

Empirical exposure-response modelling for dupilumab in participants with Chronic Spontaneous Urticaria (CTS0083)

The objectives of the PK/PD analyses were:

- To understand dupilumab E-R relationships in participants with CSU regarding key efficacy endpoints
- To identify covariates influencing the E-R relationships

Data from EFC16461 Study A and Study B were included in the analyses. For all efficacy endpoints, a total of 113 participants (55 in the dupilumab and 58 in placebo participants) from study A and 98 participants (50 in the dupilumab and 48 in the placebo) from study B were included in the PK/PD analysis.

Efficacy endpoints

The absolute change from baseline at Week 24 in weekly itch severity score (ISS7) was the primary efficacy endpoint (except EU and EU reference countries). For EU and EU reference countries, the primary efficacy endpoint was the change from baseline in weekly urticaria activity score (UAS7, composite participant reported itch and hive score).

The secondary efficacy endpoint, change from baseline in weekly hives severity score (HSS7) at Week 24, was also explored.

For participants who discontinued the study treatment due to lack of efficacy prior to Week 24, worst-observation carried forward (WOCF) approach was used to impute ISS7, UAS7 and HSS7 missing data if needed. For participants who discontinued the study treatment due to reasons other than lack of efficacy prior to Week 24: multiple imputation (MI) approach was used to impute missing endpoint value if needed, and this MI used all participants excluding participants who have taken the selected prohibited medications and/or rescue medications prior to Week 24 and excluding participants who discontinue due to lack of efficacy prior to Week 24.

For the PK/PD analysis, the participants with missing data imputed with WOCF imputation only have been added in the analysis. A sensitivity analysis was performed to test the stability of the ER model when the MI approach is used. After WOCF imputation, in study A, 4 Dupilumab and 10 placebo participants were missing and were excluded from the analysis. In study B, 4 Dupilumab and 6 placebo participants were excluded due to missing data.

Dupilumab exposure

The observed on-treatment trough concentration (Ctrough) of dupilumab at Week 24 was used in descriptive plots, summary statistics and the E-R modelling. The missing values were imputed by the values at Week 12 if available.

In addition to the participants excluded for missing efficacy endpoints, 11 dupilumab participants in study A and 4 dupilumab participants in study B were excluded from the E-R analysis due to missing PK (Ctrough) data.

Methods

Since the differences between EFC16461 Study A and Study B populations in prior therapy renders the 2 populations (omalizumab naïve versus omalizumab refractory or intolerant, respectively) distinct with respect to their CSU disease, the full pooling of efficacy data of EFC16461 Study A and Study B for the purposes of an integrated analysis of efficacy was not performed.

While the primary endpoint for Study A of ISS7 and UAS7 reduction at Week 24 met statistical significance, the efficacy results of Study B demonstrated a positive numerical trend for the primary endpoints of ISS7 and UAS7 reduction at Week 24 but missed statistical significance. Therefore, empirical model-based PK/PD analyses were conducted with data from EFC16461 Study A only.

PK/PD modelling was carried out to better understand and confirm the exposure-response relationship in Study A. For each efficacy endpoint ISS7 and UAS7, the baseline ISS7 or UAS7 value was included respectively as main effects (placebo effect) in the model. Linear, log-linear and Emax models were fitted to select the best base model by AICc. For linear and Emax models, Ctrough was set to zero for placebo participants. Ctrough was set to 0.039 which is [half of lower limit of quantification (LLOQ) for placebo participants in the log-linear model.

Covariates, either as a main effect or an interaction effect with dupilumab concentration, were explored based on the best-fitted base model. When multiple main effects and/or interaction effects were identified for inclusion consideration in the E-R model, a forward variable selection approach was used to determine the final covariates. To examine the validity of the PK/PD model, the consistency of the model predictions and observed effects was compared. In addition, for each Ctrough quartile, the PK/PD model predicted difference from placebo with its 95% CI was also presented and compared to the observed treatment difference.

Results

Descriptive statistics

- EFC16461 Study A

Scatter of individual ISS7 and UAS7 change from baseline by observed Ctrough at Week 24 are presented in Figure 12 and Figure 14, respectively, with the Ctrough quartile reference lines for participants treated with dupilumab. The scatter plots showed a generally flat relationship within the range of dupilumab concentrations.

Box plots of ISS7 and UAS7 change from baseline by observed Ctrough quartiles and placebo are presented in Figure 13 and Figure 15, respectively. The boxplots showed a decrease of the ISS7 and UAS7 change from baseline with a linear increase of Ctrough at Week 24.

Similar to ISS7 and UAS7, a generally flat E-R relationship was observed for HSS7 change from baseline at Week 24.

Figure 12. ISS7 Change from Baseline by Observed C_{trough} (mg/L) at Week 24 in EFC16461 Study A

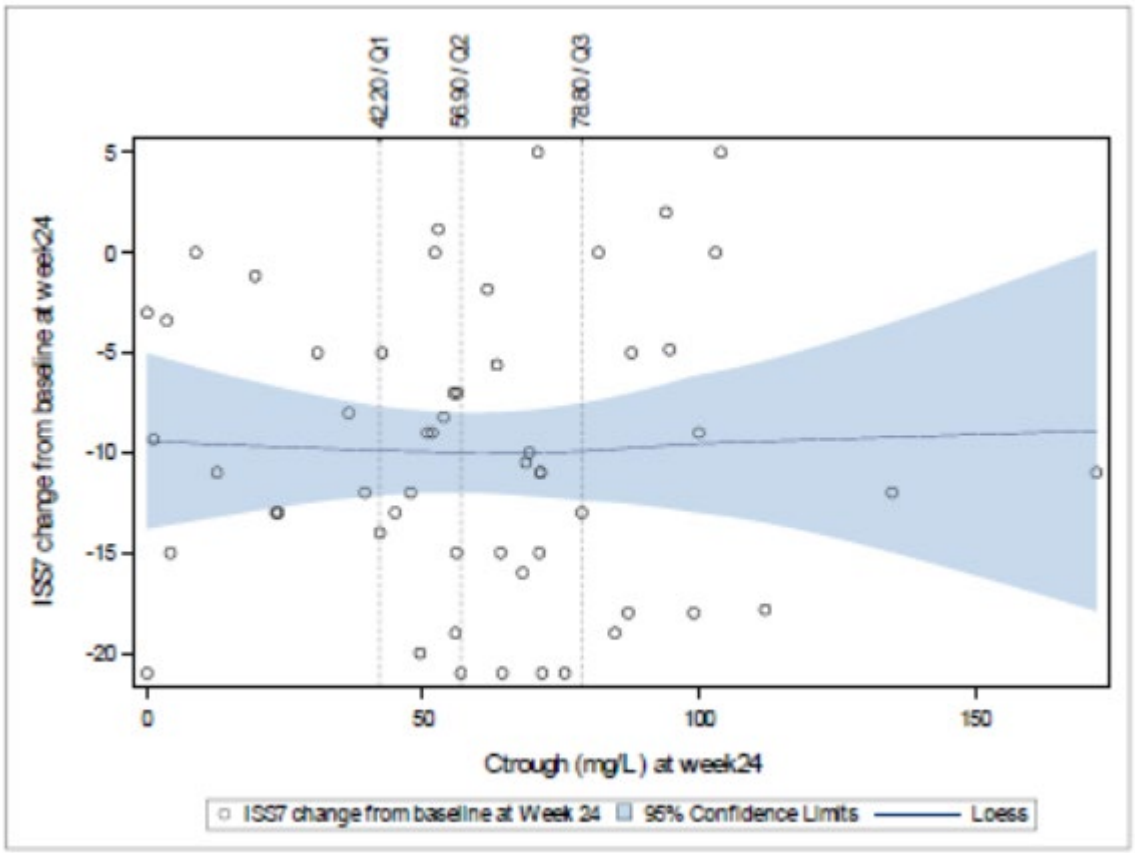


Figure 13. Boxplot of ISS7 Change from Baseline by Observed C_{trough} (mg/L) Quartiles at Week 24 and Placebo arm in EFC16461 Study A

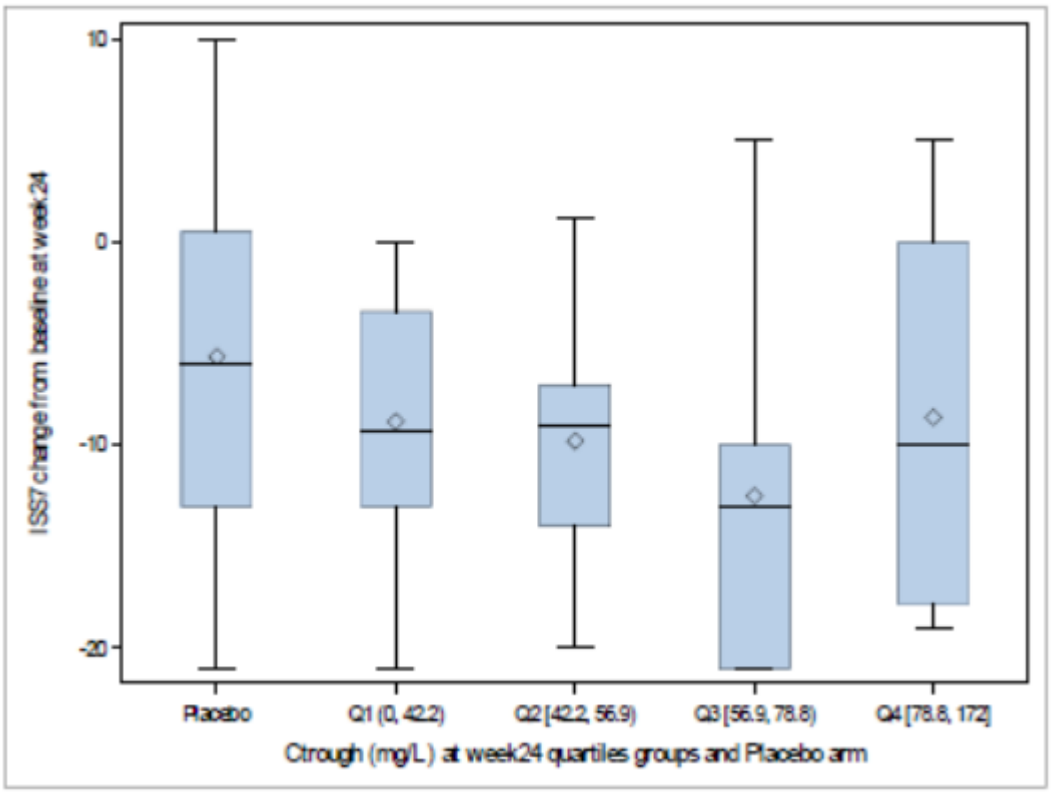


Figure 14. UAS7 Change from Baseline by Observed C_{trough} (mg/L) at Week 24 in EFC16461 Study A

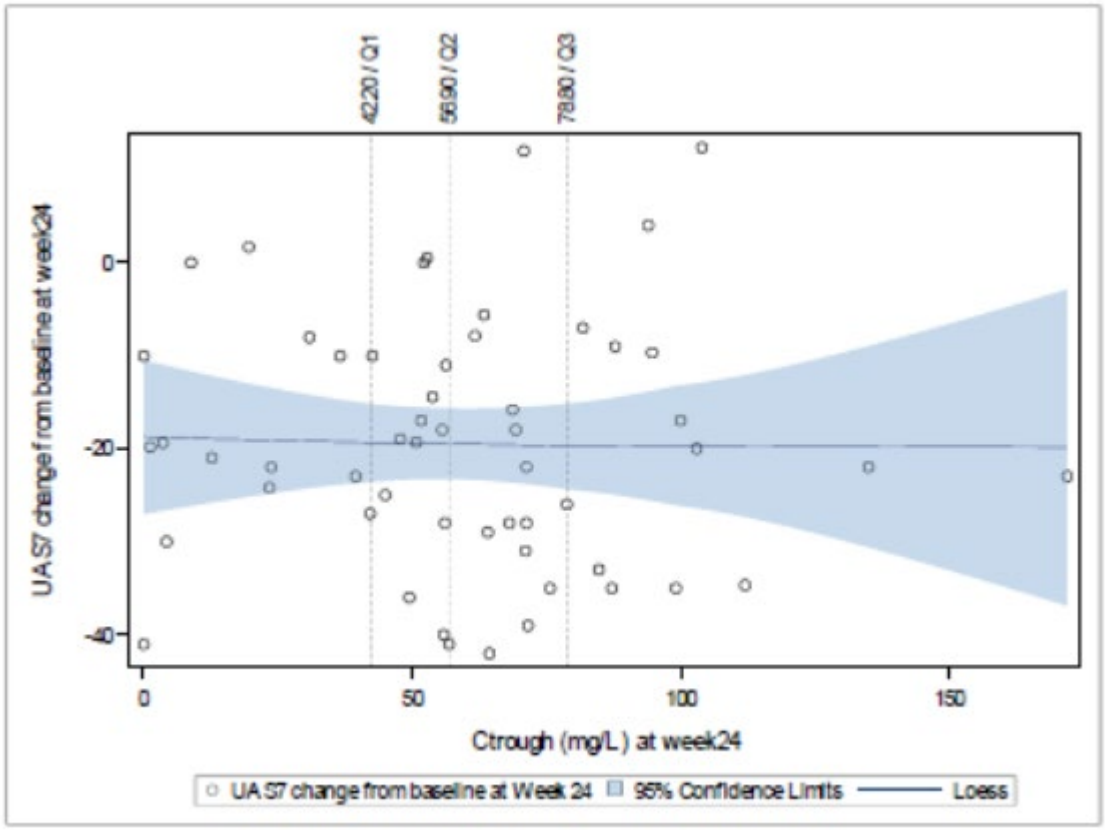
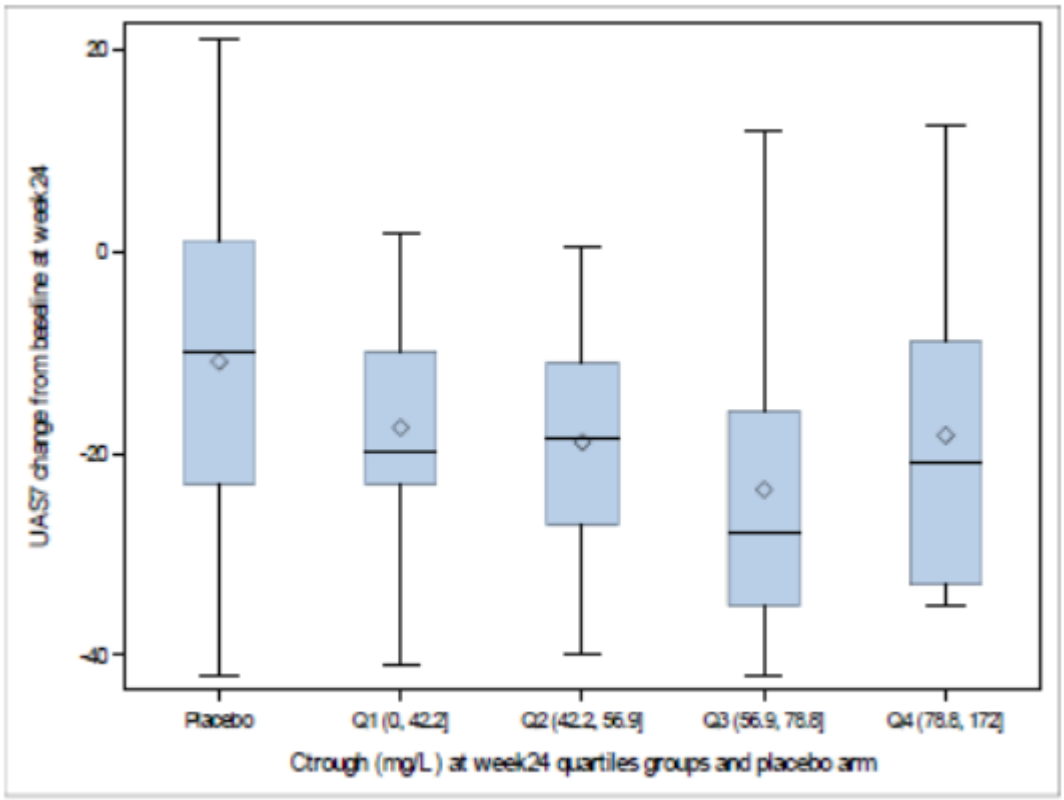


Figure 15. Boxplot of UAS7 Change from Baseline by Observed C_{trough} (mg/L) Quartiles at Week 24 and Placebo arm in EFC16461 Study A



Baseline biomarkers and baseline body weight are summarised by Ctrough quartiles in Table 10. There was no clear difference for baseline eosinophil (EOS) and H1-antihistamine (H1-AH) BL Dose % Standard Dose levels among different quartiles.

Table 10. Summary of baseline EOS, body weight and H1-AH Dose % Standard dose by Observed C_{trough} (mg/L) Quartiles at Week 24 for participants treated with Dupilumab in EFC16461 Study A

Treatment arm	C_{trough} Quartile	C_{trough} Mean (mg/L)	C_{trough} Standard Error	EOS BL mean (Giga/L)	BL weight (kg)	H1-AH BL Dose % Standard dose	Number of participants
Placebo	.			0.20	73.5	60.34	58
Dupilumab	Q1	15.73	3.9	0.18	98.0	46.15	13
Dupilumab	Q2	50.88	1.3	0.23	83.4	35.71	14
Dupilumab	Q3	67.74	1.3	0.16	72.7	42.86	14
Dupilumab	Q4	102.44	6.6	0.13	59.0	50.00	14

Abbreviations: BL: baseline; Ctrough: trough concentration; EOS: eosinophils; H1-AH: H1-antihistamine.
Quartile values: Q1= 42.20; Q2= 56.90 ; Q3= 78.80 mg/L for dupilumab; N=13 to 14 per quartile.

- EFC16461 Study B

Scatter of individual ISS7 and UAS7 change from baseline by observed Ctrough at Week 24 are presented in Figure 16 and Figure 18, respectively. The scatter plots showed a generally flat relationship within the range of dupilumab concentrations in participants treated with dupilumab

Box plots of ISS7 and UAS7 change from baseline by observed Ctrough quartiles and placebo are presented in Figure 17 and Figure 19, respectively.

Similar to ISS7 and UAS7, a generally flat E-R relationship was observed for HSS7 change from baseline at Week 24.

Figure 16. ISS7 Change from Baseline by Observed C_{trough} (mg/L) at Week 24 in EFC16461 Study B

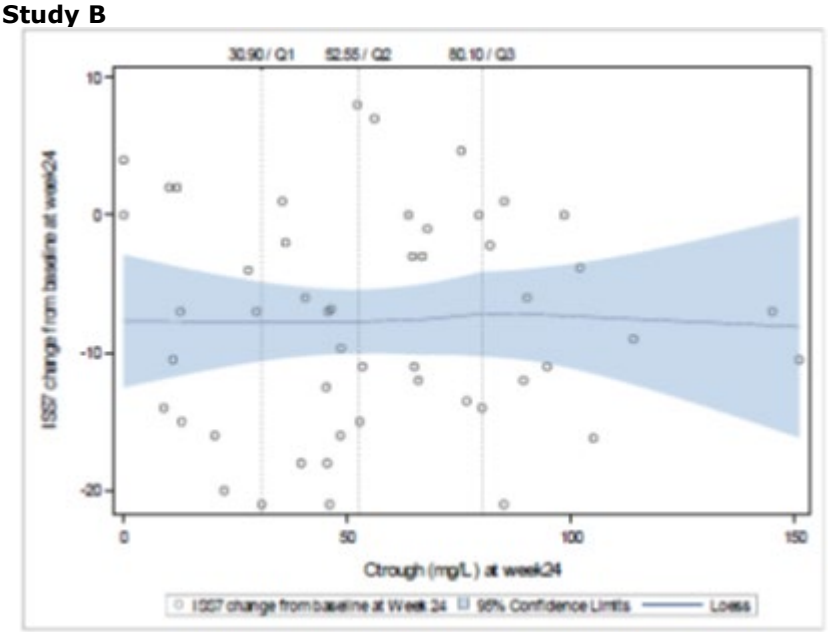


Figure 17. Boxplot of ISS7 Change from Baseline by Observed C_{trough} (mg/L) Quartiles at Week 24 and Placebo arm in EFC16461 Study B

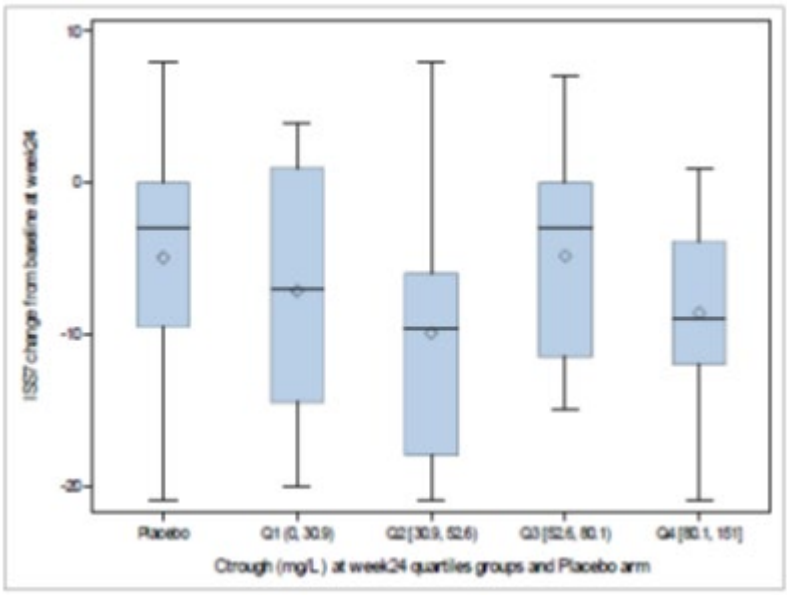


Figure 18. UAS7 Change from Baseline by Observed C_{trough} (mg/L) at Week 24 in EFC16461 Study B

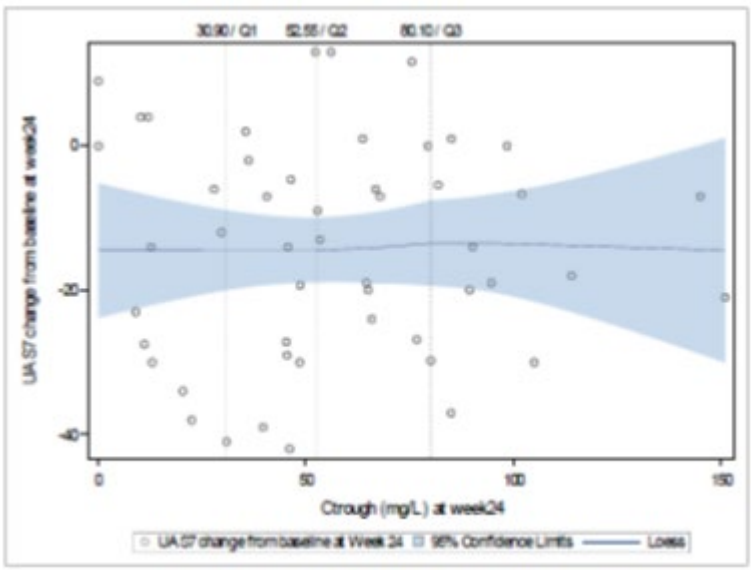
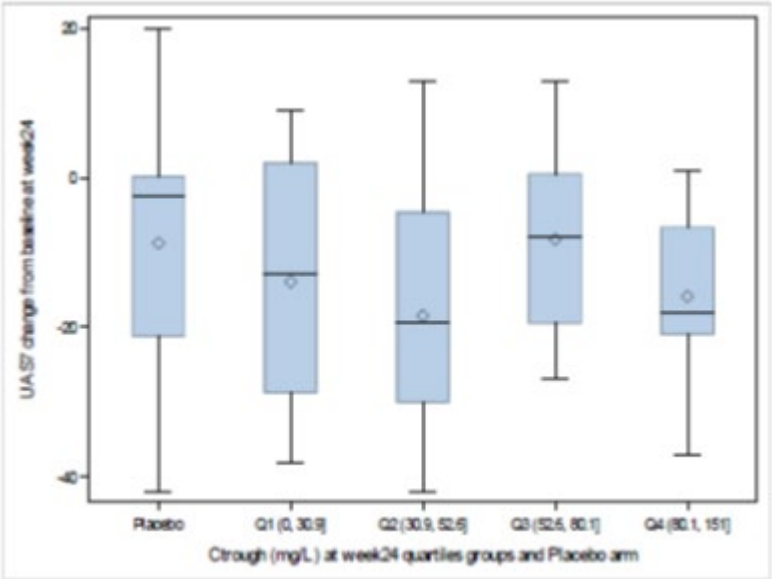


Figure 19. Boxplot of UAS7 Change from Baseline by Observed C_{trough} (mg/L) Quartiles at Week 24 and Placebo arm in EFC16461 Study B



Baseline biomarkers and baseline body weight are summarised by Ctrough quartiles in Table 11. There was no clear difference for baseline EOS and H1-AH BL Dose % Standard Dose levels among different quartiles.

Table 11. Summary of baseline EOS and body weight by Observed C_{trough} (mg/L) quartiles at Week 24 for participants treated with Dupilumab in EFC16461 Study B

Treatment arm	C_{trough} Quartile	C_{trough} Mean at W24	C_{trough} Standard Error	EOS BL mean (Giga/L)	BL weight (kg)	H1-AH BL Dose % Standard Dose	Number of Participants
Placebo	.			0.13	74.4	31.91	48
Dupilumab	Q1	14.05	2.7	0.16	89.9	33.33	12
Dupilumab	Q2	43.18	1.7	0.21	86.8	38.46	13
Dupilumab	Q3	65.65	2.5	0.13	77.4	41.67	12
Dupilumab	Q4	101.68	6.3	0.14	69.3	30.77	13

Abbreviations: BL: baseline; C_{trough}: trough concentration; EOS: eosinophils; H1-AH: H1-antihistamine; UAS7: urticaria activity score over 7 days.
Quartile values : Q1= 30.90 ; Q2= 52.55 ; Q3= 80.10 mg/L

Empirical models (EFC16461 Study A)

- ISS7

A log-linear model was selected as the best base model according to AICc (=760.53 for a log-linear model vs 763.04 and 765.19 for a linear model and an Emax model, respectively). After a forward selection H1-AH Baseline Dose only was included in the base model with baseline ISS7. The log-linear model showed that the change from baseline decreased with a linear increase of Ctrough at Week 24. In addition, the change decreases as baseline ISS7 Score ($p < 0.0001$) increases. The H1-AH Baseline Dose (4-fold standard dose vs. other) was associated with ISS7 effects response in the placebo group (placebo effect rate) regardless of the treatment. The ISS7 change from baseline increases with H1-AH Baseline Dose=4-fold standard dose ($p=0.059$).

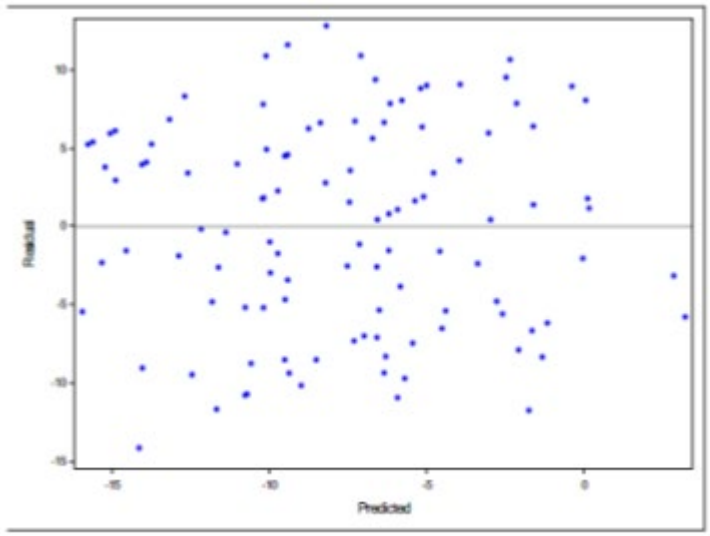
Parameter estimates of the final PK/PD model are presented in Table 12. The residual by predicted value plot did not show any pattern of lack of fit (Figure 20).

Table 12. ISS7 Change from Baseline at Week 24: The PK/PD Model parameters estimates

Parameter	Estimate	95%CI	Standard Error	P-value
b0	-8.326	(-9.757, -6.895)	0.722	<.0001
b1: Baseline ISS7 Score	-0.743	(-1.052, -0.434)	0.156	<.0001
b2: H1-AH Baseline Dose [4-fold standard dose]	3.163	(-0.131, 6.457)	1.663	0.0597
b3: EOS	2.741	(-5.24, 10.721)	4.028	0.4976
bpk1:	-0.721	(-1.082, -0.359)	0.183	0.0001
bpk2: EOS	2.267	(-0.002, 4.536)	1.145	0.0502
sigma**2	42.81	(31.475, 54.145)	5.721	<.0001

Abbreviations: EOS= Baseline Eosinophils (10/L)
ISS7 change = b0 + b1*(baseline ISS7 score -median baseline ISS7 score) + b2*(H1-AH Baseline Dose [4-fold standard dose]) + b3*(EOS-median EOS) + (bpk1 + bpk2*(EOS-median EOS))*log(Ctrough)
Base model: N=112, AICC=754.69
Model without Eosinophils interaction: N=112, AICC=753.14
Model with EOS interaction with Ctrough: N=112, AICC=753.68

Figure 20. ISS7 Change from Baseline: PK/PD Model Residual vs. Predicted Values at Week 24



The PK/PD model predicted ISS7 change from placebo versus Ctrough overlaying the observed treatment differences are presented for dupilumab group and by dupilumab concentration quartiles in Table 13 and Table 14, respectively. The predicted placebo adjusted ISS7 change from baseline is presented in Figure 21. The predicted mean difference and the predicted curve showed greater reduction in ISS7 with increasing dupilumab Ctrough at Week 24 and appeared to plateau at the exposure of 2nd quartile Q2 (mean Ctrough of 51.95 mg/L). The results of the sensitivity analysis for missing ISS7 values (with and without MI) were similar.

Table 13. ISS7 Change from Baseline: Observed and PK/PD Model Predicted Treatment Differences at Week 24

Comparison vs Placebo	Observed PD LS Mean Difference (95% CI) from ANCOVA Model	Predicted Mean Difference (95% CI) from PK/PD Model	Median C_{trough} (mgL) at Week 24
Dupilumab	-4.472 (-7.129, -1.814)	-5.086 (-7.721, -2.451)	56.9

Predicted based on the final PK/PD model and median baseline covariates.

Observed effects were based on PD analysis of observed ISS7 change at Week 24 as response and the treatment arm, ISS7 at baseline, region (Asia, East Europe, Latin America and Western Countries) and Angioedema at Baseline (Y/N) as covariates.

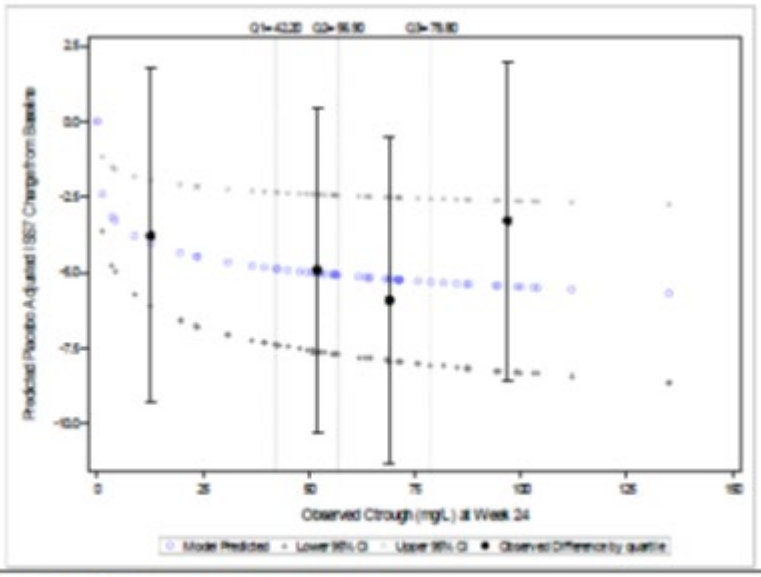
Table 14. ISS7 Change from Baseline: Observed and PK/PD Model Predicted Treatment Differences at Week 24 by C_{trough} quartiles groups

Quartile Comparison vs Placebo	Observed PD LS Mean Difference (95% CI) from ANCOVA Model	Predicted Mean Difference (95% CI) from PK/PD Model	Median C_{trough} (mgL) at Week 24
Q1	-3.785 (-9.318, 1.748)	-4.039 (-6.132, -1.946)	12.7
Q2	-4.925 (-10.309, 0.459)	-5.022 (-7.624, -2.42)	51.95
Q3	-5.919 (-11.296, -0.542)	-5.22 (-7.925, -2.516)	69
Q4	-3.286 (-8.562, 1.991)	-5.457 (-8.285, -2.63)	96.9

Predicted based on the final PK/PD model and median baseline covariate.

Observed effects were based on PD analysis of observed ISS7 change at Week 24 as response and the quartiles group, ISS7 at baseline, region (Asia, East Europe, Latin America and Western Countries) and Angioedema at Baseline (Y/N) as covariates.

Figure 21. PK/PD Model Predicted ISS7 change from Baseline versus observed C_{trough} and Observed Treatment Differences



Predicted based on the final PK/PD model and median baseline covariate.

Observed effects were based on PD analysis of observed ISS7 change at Week 24 as response and the quartiles group, ISS7 at baseline, region (Asia, East Europe, Latin America and Western Countries) and Angioedema at Baseline (Y/N) as covariates.

- UAS7

A log-linear model was selected as the best base model according to AICc (=910.99 for a log-linear model vs 912.52 and 913.1 for a linear model and an Emax model, respectively). The log-linear base PK/PD model showed that the change from baseline decreased with a linear increase of Ctrough at Week 24. In addition, the change decreases as baseline UAS7 Score (p=0.0001) increases.

The H1-AH Baseline Dose (4-fold standard dose vs. other) was associated with UAS7 effects response in the placebo group (placebo effect rate) regardless of the treatment. The number of Angioedema episodes east 6 months was removed due to the high number of missing values. The UAS7 change from baseline increases with H1-AH Baseline Dose=4-fold standard dose (p=0,051). Baseline EOS (p-value=0.12) and all the others baseline covariates interaction effects were not significant.

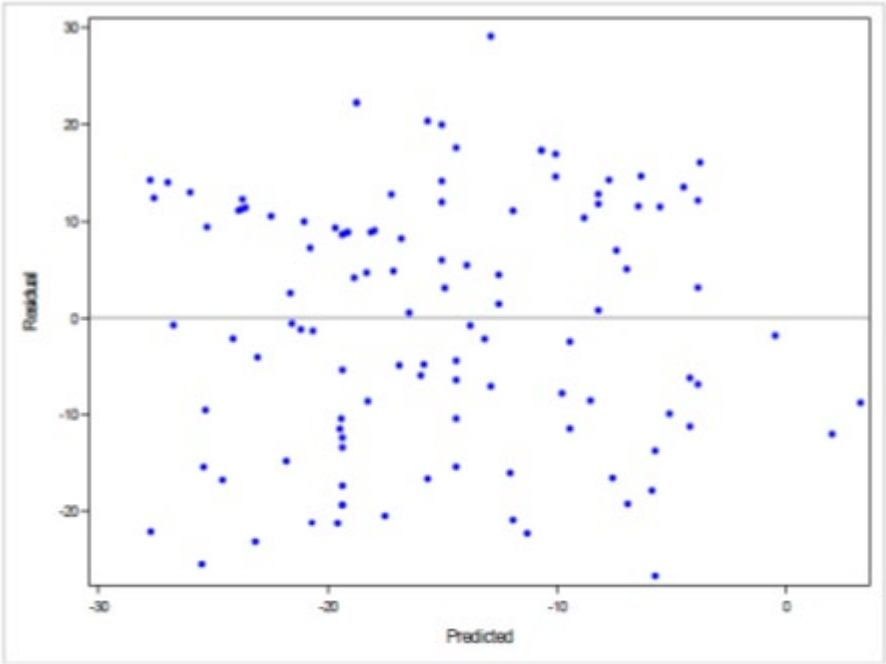
Parameter estimates of the final PK/PD model are presented in Table 15. The residual by predicted value plot did not show any pattern of lack of fit (Figure 22).

Table 15. UAS7 Change from Baseline at Week 24: The PK/PD Model parameters estimates

Parameter	Estimate	95%CI	Standard Error	P-value
b0	-16.209	(-18.89, -13.528)	1.353	<.0001
b1: Baseline UAS7 Score	-0.62	(-0.939, -0.302)	0.161	0.0002
b2: H1-AH Baseline Dose [4-fold standard dose]	6.48	(-0.036, 12.996)	3.289	0.0513
bpk:	-1.131	(-1.804, -0.458)	0.34	0.0012
sigma**2	169.106	(124.534, 213.677)	22.498	<.0001

UAS7 change = b0 + b1*(baseline UAS7 score -median baseline UAS7 score) + b2*(H1-AH Baseline Dose [4-fold standard dose]) + bpk*log (Ctrough).
Base model: N=113, AICC=912.62
Final Model: N=113, AICC=910.99

Figure 22. UAS7 Change from Baseline: PK/PD Model Residual vs. Predicted Values at Week 24



The PK/PD model predicted UAS7 change from placebo versus Ctrough overlaying the observed treatment differences are presented for dupilumab group and by dupilumab concentration quartiles in Table 16 and Table 17, respectively. The predicted placebo adjusted UAS7 change from baseline is presented in Figure 23. The predicted mean difference and the predicted curve showed UAS7 reduction with increasing dupilumab Ctrough at Week 24 and appeared to plateau at the exposure of 2nd quartile Q2 (mean Ctrough of 51.95 mg/L). The results of the sensitivity analysis for missing UAS7 values (with and without MI) were not reported.

Table 16. UAS7 Change from Baseline: Observed and PK/PD Model Predicted Treatment Differences at Week 24

Comparison vs Placebo	Observed PD LS Mean Difference (95% CI) from ANCOVA Model	Predicted Mean Difference (95% CI) from PK/PD Model	Median C_{trough} (mg/L) at Week 24
Dupilumab	-8.23 (-13.384 , -3.076)	-8.24 (-13.141, -3.339)	56.9

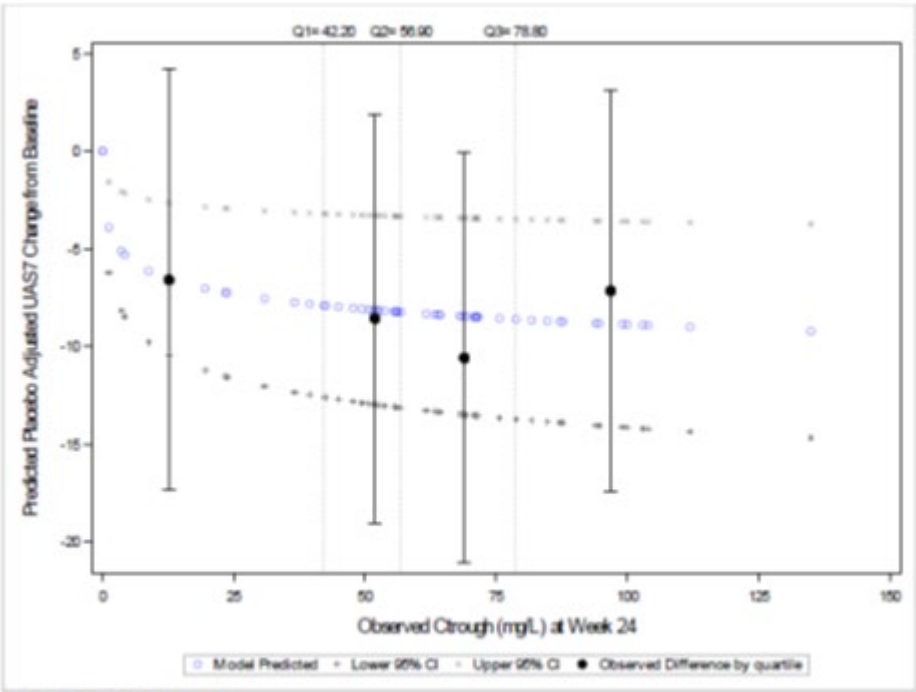
Predicted based on the final PK/PD model and median baseline covariates.
Observed effects were based on PD analysis of observed UAS7 change at Week 24 as response and the treatment arm, UAS7 at baseline, region (Asia, East Europe, Latin America and Western Countries) and Angioedema at Baseline (Y/N) as covariates.

Table 17. UAS7 Change from Baseline: Observed and PK/PD Model Predicted Treatment Differences at Week 24 by C_{trough} quartiles groups

Quartile Comparison vs Placebo	Observed PD LS Mean Difference (95% CI) from ANCOVA Model	Predicted Mean Difference (95% CI) from PK/PD Model	Median C_{trough} (mg/L) at Week 24
Q1	-6.593 (-17.364, 4.179)	-6.544 (-10.436, -2.651)	12.7
Q2	-8.57 (-19.045, 1.905)	-8.137 (-12.976, -3.297)	51.95
Q3	-10.59 (-21.1, -0.079)	-8.458 (-13.488, -3.427)	69
Q4	-7.155 (-17.431, 3.121)	-8.842 (-14.101, -3.583)	96.9

Predicted based on the final PK/PD model and median baseline covariate.
Observed effects were based on PD analysis of observed UAS7 change at Week 24 as response and the quartiles group, UAS7 at baseline, region (Asia, East Europe, Latin America and Western Countries) and Angioedema at Baseline (Y/N) as covariates.

Figure 23. PK/PD Model Predicted UAS7 change from Baseline versus observed Ctrough and Observed Treatment Differences



Predicted based on the final PK/PD model.
Observed effects were based on PD analysis of observed UAS7 change at Week 24 as response and the treatment arm, UAS7 at baseline region (Asia, East Europe, Latin America and Western Countries) and Angioedema at Baseline (Y/N) as covariates.

Pharmacokinetic (PK), pharmacodynamic (PD) and immunogenicity data were collected in the two pivotal Phase 3 studies in patients with CSU (EFC16461 Study A and Study B).

Population pharmacokinetic analysis of dupilumab using pooled data from Phase 3 studies in patients with Chronic Spontaneous Urticaria (POH0861)

The Pop PK analysis was based on pooled data from the two Phase 3 studies in patients with CSU (EFC16461 Study A and Study B). The methods and data exclusions are acceptable.

A global Pop PK base model, previously developed from HV, AD and asthma populations, was applied to the sparse PK data collected in patients with CSU. A MAP Bayesian approach was used to generate individual PK parameters and post hoc PK exposures. This approach is acceptable given the PK similarity of dupilumab across different patient populations.

Model diagnostics showed good agreement between observed dupilumab concentration data and model-predicted dupilumab concentrations in patients with CSU. The predictive performance of the model is considered adequate for performing dosing simulations in patients with CSU.

The mean model-predicted post hoc trough concentration at steady-state appears similar to the mean observed trough concentration, for the 300 mg q2w regimen. It is not feasible to evaluate similarity between model-predicted post-hoc and observed trough concentrations for the 200 mg q2w regimen since only one patient who received this dose had PK data. However, PK simulations demonstrated that the 300 mg q2w dose regimen (≥60 kg) and the 200 mg q2w (30 to <60 kg) in adolescents with CSU would achieve dupilumab exposure similar to that for the 300 mg q2w dose regimen in adult patients with CSU, and similar to the exposure observed in adult and adolescent patients with AD treated with the approved dose regimens 200 mg q2w (30 to <60 kg) and 300 mg q2w (≥60 kg). Thus, the simulation results support the proposed dose regimens for adolescent and adult patients with CSU.

The influence of selected intrinsic and extrinsic factors on dupilumab PK in patients with CSU was evaluated by the comparison of post hoc estimates of PK exposures. Consistent with the finding in other populations, body weight was identified as the main factor explaining dupilumab PK variability in CSU patients. The magnitude of the body weight effect on dupilumab exposure is not considered likely to yield a clinically meaningful effect on efficacy given the relatively flat exposure-response relationships. Therefore, no further dose adjustment based on body weight is considered necessary.

According to the Applicant, all other tested covariates, including baseline demographics (gender, age, and race), baseline lab parameters (creatinine clearance and albumin), immunogenicity, ethnicity, patient population (with or without omalizumab treatment), baseline biomarker and disease characteristics (ISS7, UAS7, HSS7) and concomitant medication (H1AH), had no apparent effect on dupilumab PK exposure in patients with CSU. This is generally agreed. However, there does appear to be some effect of ADA status on dupilumab exposure, but this observation is limited by low patient numbers. Overall, no dose adjustment is warranted for any intrinsic factors.

Total IgE in serum

Total IgE in serum was assessed in CSU patients in EFC16461 Study A and Study B. A continuous decline in total IgE was observed over the dupilumab treatment period compared to no apparent change in patients who received placebo. It is agreed that the decline in total IgE in adolescent CSU patients was similar. However, the number of adolescent subjects was too small to make any firm conclusion. The effect of dupilumab on total IgE over time appeared to be of similar magnitude in CSU, AD, asthma, CRSwNP, EoE and PN patient populations. Whether or not reduction in IgE is associated with efficacy in patients with CSU was not evaluated.

Immunogenicity

Based on pooled data from EFC16461 Study A and Study B, the incidence of treatment-emergent ADAs through Week 24 (on-treatment period) was reasonably low (6.6% in the dupilumab group compared

to 0.8% in the placebo group). The incidence of persistent ADAs through Week 24 was 0.8% and 0%. Overall, no clear evidence of an impact of ADAs (including Nabs) on dupilumab exposure, efficacy or safety was observed in CSU patients. However, it is not feasible to draw any definitive conclusions on the impact of ADAs because of the small number of subjects who developed ADAs.

Empirical exposure-response modelling for dupilumab in participants with Chronic Spontaneous Urticaria (CTS0083)

Using data collected in EFC16461 Study A and Study B, PKPD analyses were conducted to explore dupilumab E-R relationships in patients with CSU. Observed dupilumab Ctrough concentrations at Week 24 were used as the PK metric with efficacy endpoints of UAS7, ISS7 and HSS7. The data from each study were not pooled due to differences between the two study populations. Both descriptive (Study A and Study B) and model-based approaches (Study A only) were conducted.

For the descriptive analyses, no E-R relationship could be observed for each of the efficacy endpoints (UAS7, ISS7 and HSS7) at the dupilumab steady-state trough concentrations achieved in Study A and Study B.

Log-linear models provided the best fit to the PK/PD data for both efficacy endpoints (UAS7 and ISS7) in Study A. The developed empirical models showed a reduction in UAS7 and ISS7 with increasing dupilumab Ctrough and the E-R relationships of UAS7 and ISS7 change from baseline were similar. However, the relationships were shallow with the response appearing to plateau in the 2nd exposure quartile (mean Ctrough ~51 mg/L). For both PD endpoints, body weight, ADA status, baseline angioedema, and baseline total IgE were not found to have a significant interaction effect with exposure.

Given that the simulated Ctrough,ss of the 300 mg q2w/200 mg q2w dosing regimens in adolescents was similar to that of 300 mg q2w in adults with CSU, the efficacy responses would be expected to be comparable between adolescents and adults with CSU. However, this is based on the assumption that the pathogenesis of CSU in adolescents is similar to that in adults.

2.3.5. Conclusions on clinical pharmacology

Pharmacokinetic (PK), pharmacodynamic (PD) and immunogenicity data were collected in two Phase 3 studies in patients with CSU (EFC16461 Study A and Study B). These data were analysed in Pop PK and PK/PD analyses. In terms of Clinical Pharmacology, no major objections were raised. A number of other concerns relating to the Pop PK analysis were raised and these have been resolved. Simulations based on the PopPK model indicated that the proposed dupilumab dosage regimens for adolescents are predicted to achieve similar dupilumab exposure to adults.

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 is based on pivotal **Study B** and a supportive **Study A** in two subsets of CSU patients who remain symptomatic despite the use of H1-antihistamine treatment. Study B included patients who were intolerant or incomplete responders to omalizumab, while in study A patients were naïve to omalizumab.

Both studies were similarly designed phase 3 studies; multinational, multicenter, randomized, parallel-group, double-blind, placebo-controlled studies with a 24-week treatment period. The studies were conducted under one master protocol (**EFC16461**) and enrolled participants aged 12 years to 80 years.

Table 18. Overview of Phase 3 CSU studies evaluated in the Summary of Clinical Efficacy

Study number/ status	Study objective	Treatment/ follow-up duration	Participants randomized/ treated
Phase 3			
EFC16461 (CUPID) Study B Completed 5.3.5.1 [EFC16461 Study B]	Efficacy and safety of dupilumab compared to placebo in omalizumab intolerant or incomplete responder participants with CSU who remain symptomatic despite the use of H1-antihistamines. (Primary endpoint: Change from baseline in UAS7 [composite patient reported itch and hive score] at Week 24. Main key secondary endpoint: Change from baseline in ISS7 at Week 24).	24/12 weeks	Randomized/treated: 108/108 (Dupilumab: 54[a], Placebo: 54[a])
EFC16461 (CUPID) Study A Completed 5.3.5.1 [EFC16461 Study A]	Efficacy and safety of dupilumab compared to placebo in participants with CSU who remain symptomatic despite the use of H1-antihistamines. (Primary endpoint: Change from baseline in UAS7 [composite patient reported itch and hive score] at Week 24. Main key secondary endpoint: Change from baseline in ISS7 at Week 24).	24/12 weeks	Randomized/treated: 138/138 (Dupilumab: 70[a], Placebo: 68[a])

CSU: Chronic spontaneous urticaria; ISS7: Itch severity score over 7 days; UAS7: Urticaria activity score over 7 days.
a As treated

2.4.2.1. EFC16461 Study B

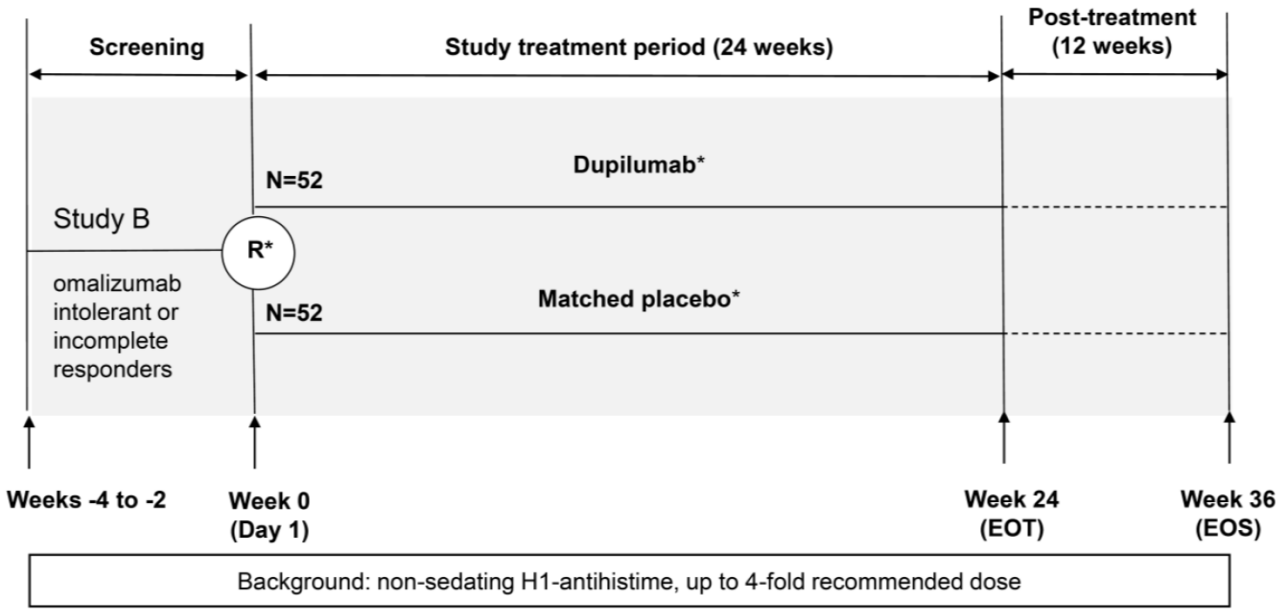
EFC16461 Study B was a 24-week, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of dupilumab in adult and adolescent participants with CSU who remained symptomatic despite the use of H1-antihistamine and who were intolerant or incomplete responders to omalizumab.

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)

Figure 24. Overview on the study design for study B



Dupilumab 300 mg q2w, administered as 1 SC injection of dupilumab 300 mg (2 mL)
Dupilumab 200 mg q2w, administered as 1 SC injection of dupilumab 200 mg (1.14 mL)
Matched placebo is prepared in the same formulation without the addition of the active substance
A loading dose equivalent to treatment group assigned will be administered on Day 1.

* Adults: 300 mg q2w; Adolescents: 200 mg q2w if <60 kg or 300 mg q2w if >60 kg

Abbreviations: EOS = end-of-study; EOT = end-of-treatment; R = randomization; SC = subcutaneous; q2w = every 2 weeks

Study participants

Key inclusion criteria were:

- Participants ≥12 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 intolerant or incomplete responders**

*Per protocol, participants should remain on their prescreening non-sedating H1-AH dose. Only up to 4 fold the recommended dose is allowed. If participants are on dose higher than 4-fold the recommended dose at screening, the Investigator can adjust the participant dose to the stipulated range at the screening visit.

** Participants were considered as intolerant or incomplete responders to omalizumab if they were treated for CSU with at least 300 mg (q4w) of omalizumab for at least 3 months (minimum of injections) and had an inadequate response or were intolerant, resulting in treatment discontinuation,

as confirmed by Investigator assessment. Information about intolerance or incomplete response to omalizumab had to be well documented in the patient´s medical records.

Key exclusion criteria were:

- Body weight less than 30 kg in adults and adolescents.
- 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.
- Severe concomitant illness(es) that, in the Investigator's judgment, would adversely affect the patient's participation in the study.
- Diagnosed active endoparasitic infections; suspected or high risk of endoparasitic infection, unless clinical and (if necessary) laboratory assessment have ruled out active infection before randomization.
- Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiprotozoals, or antifungals within 2 weeks before the screening visit and during the screening period.
- Known or suspected immunodeficiency, including history of invasive opportunistic infections.
- History of systemic hypersensitivity or anaphylaxis to any biologic therapy.
- Patient with any other medical or psychological condition including relevant laboratory or electrocardiogram abnormalities at screening that, in the opinion of the Investigator, suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study participant as a result of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments.
- Current history of substance and/or alcohol abuse.
- 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 (adults and those adolescents ≥60 kg)

Dupilumab 200 mg q2w (adolescents <60 kg)

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). If participants were on a dose higher than 4-fold (2-fold in Japan) the recommended dose at screening visit, the Investigator had to adjust the participant dose within the stipulated range at the screening visit. 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.

Objectives

Primary objective:

- To demonstrate the efficacy of dupilumab in study participants with CSU who remain symptomatic despite the use of H1-antihistamines in omalizumab intolerant or incomplete responders

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 (EU and EU reference countries). The primary efficacy endpoint was evaluated at Week 24 in both studies.

Secondary objectives

- To demonstrate the efficacy of dupilumab on the reduction of itch severity (ISS7)
- To demonstrate the efficacy of dupilumab on reduction of hives severity (HSS7)
- To demonstrate the efficacy of dupilumab on urticaria control
- To demonstrate the efficacy of dupilumab on angioedema
- To demonstrate improvement in health-related quality of life and overall disease status and severity
- To evaluate the ability of dupilumab in reducing the proportion of patients who require treatment with OCS

Outcomes/endpoints

Primary endpoint:

- Change from baseline in weekly urticaria activity score (UAS7, composite patient reported itch and hive score) at Week 24

Secondary endpoints (multiplicity controlled):

- Change from baseline in ISS7 at Week 24

- Change from baseline in HSS7 at Week 24
- Proportion of participants with ISS7 ≥5 response at Week 24
- Proportion of patients with UAS7 ≤6 at Week 24
- Proportion of patients with UAS7 =0 at Week 24
- Change from baseline in UCT at Week 24

Other secondary endpoints

- Change from baseline in angioedema activity score over 7 days (AAS7) at Week 12 and Week 24
- Time-to-event and proportion of patients receiving OCS for CSU during the planned treatment period
- Change from baseline in Dermatology Life Quality Index (DLQI) in patients ≥16 years old, and in Children's Dermatology Life
- Quality Index (CDLQI) in patients ≥6 to <16 years old at Week 12 and Week 24
- Patient Global Impression of Change (PGIC) of CSU at Week 12 and Week 24
- Change from baseline in Patient Global Impression of Severity (PGIS) of CSU at Week 12 and Week 24

Sample size

An absolute change of 10 in the weekly urticaria activity score (UAS7) was considered the minimal clinically important difference (MDD). Based upon a SD of 14, a change of 10 in the UAS7 would correspond to an effect size of approximately 0.7. Based on this assumption, plus the assumption of a 15% dropout rate, a 2-sided t-test with alpha = 0.05 has a power of 90% (to reject the null hypothesis of equal group means) if the effect size is 0.7 (between the dupilumab arm and placebo) and 52 patients per group are included. This sample size estimate applies to both ISS7 (primary endpoint for all countries except EU and EU reference countries) and UAS7 (primary endpoint for EU and EU reference countries).

Considering the reduced drop-out rate of 10% observed during the study, an interim analysis had been performed when the first 83 randomized patients had completed their Week 24 visit by the interim analysis cut-off date. Using the O'Brien-Fleming approach with information fraction 0.77 and overall type-I error controlled at 0.05, the alpha spending at this interim analysis was 0.021, and the alpha spending at the final analyses when all 108 patients completed the study was 0.043.

At the interim analysis, it was estimated that 42 patients per group would provide 77% power to detect a treatment effect of 10 or higher with SD 14 and MDD of approximately 7.4 for UAS7 between the dupilumab arm and placebo using a 2-sided t-test with alpha = 0.021.

The overall power for the study was approximately 88%.

Randomisation

All participants were centrally assigned to randomized study intervention using an interactive response technology (IRT). Sanofi generated the randomized intervention kit number list centrally and IMPs

(dupilumab 300 mg, dupilumab 200 mg, or their matching placebo) are packaged in accordance with this list. The IRT generated the participant randomization list and allocated the intervention number and the corresponding intervention kits to the participants according to it.

Participants were randomized in a 1:1 ratio to intervention or control group, respectively.

The randomization was stratified first by age (adults versus adolescents; up to approximately 5% of total sample size for adolescents). In adults, randomization was stratified further by country. In adolescents/children ≥6 to <12 years of age, randomization was not stratified further.

A randomized participant was defined as a participant who has been allocated to a randomized intervention regardless whether the treatment was administered or not (ie, participant registered by the IRT).

Blinding (masking)

This was a double-blind study.

Dupilumab 300 mg/200 mg and placebo matching dupilumab 300 mg/200 mg was provided in identically matched 2 mL/1.14 mL pre-filled syringes that are visually indistinguishable for each dose. Syringes and box was labeled with a treatment kit number. While these were double-blind

trials with regard to the treatment with either dupilumab or placebo, they were not blinded to weight based dose levels, due to the different volume size (2 mL versus 1.14 mL) of the dose level of dupilumab (300 mg/matching placebo or 200 mg/matching placebo) that were used for the different weight categories for adolescents and children ≥6 to <12 years of age. In addition, in children, the study was not blinded to dose regimen due to the different frequency of IMP administration (q4w versus q2w).

In addition, to maintain the study integrity following the interim analysis (IA) with respect to subsequent study conduct and/or data analyses, a dissemination plan was prepared prior to IA database lock to clearly define and set up 2 separate study teams (blinded and unblinded), an independent-to-Sponsor statistical group for IA, and an independent-to-Sponsor Interim Analysis Review Committee (IARC). For the 2 separate study teams, appropriate steps were implemented to ensure that the study remained blinded to all individuals involved in the conduct of the study and/or analysis after the IA, and to protect the overall blinding and integrity of the Study B data following the IA. The IA was performed by the independent-to-Sponsor statistical group and the IA results were reviewed by the independent-to-Sponsor IARC. The IARC was responsible for analyzing and reviewing the interim efficacy results and providing guidance on the outcome (ie, “efficacy at IA”, “stop for futility”, or “continue up to EOT for the primary analysis”).

Statistical methods

Analysis Populations

Population	Description
Screened	All participants who sign the ICF
Randomized	All participants from the screened population who have been allocated to a randomized intervention by IRT regardless of whether the treatment kit was used or not. Participants treated without being randomized will not be considered randomized and will not be included in any efficacy population.
Intent-to-treat (ITT)	All randomized participants analyzed according to the intervention group allocated by randomization.
Intent-to-treat24 (ITT24) (For interim analysis)	First 83 participants who were randomized and would have completed the Week 24 visit.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received. Randomized participants for whom it is unclear whether they took the study medication will be included in the safety population as randomized. For participants who accidentally receive a different intervention from that which was planned, the actual intervention allocation for as-treated analysis will be the dupilumab group. The pharmacodynamic (PD) analyses will be performed on the safety population.

Primary and secondary Estimands

The primary analysis population for the efficacy endpoints was the ITT population.

Table 19. Selected prohibited and/or rescue medications impact on efficacy

Medication	Comment	Intervention in the main statistical analysis (Yes/No)[a] / Selection criteria
Systemic immunosuppressants (immunosuppressive/immunomodulating drugs) eg, systemic corticosteroids (oral or parenteral [intravenous, intramuscular, SC]), cyclosporine, mycophenolate-mofetil, interferon gamma, Janus kinase inhibitors, azathioprine, methotrexate, hydroxychloroquine, dapsone, sulfasalazine, colchicine, etc.	IMP to be discontinued	Yes (Standardized drug groupings (SDGs) Other immunosuppressants, tumour necrosis factor (TNF) alpha inhibitors, Calcineurin inhibitors, Interleukin inhibitors, Selective immunosuppressants – all Narrow)
Antifibrinolytic tranexamic acid and epsilon-aminocaproic acid		No
Other monoclonal antibodies (which are biological response modifiers).		Yes (SDG Monoclonal antibodies Narrow)
Phototherapy, including tanning beds.		No
IVIG		Yes (CDG00488 Intravenous immunoglobulin therapy - See Section 5.6)
Plasmapheresis		Yes (CMQ00079 based on the following PTs: Plasmapheresis, Apheresis)
Other investigational drugs.		No, except ones with mechanism of action that may impact efficacy
Topical corticosteroids.	No IMP discontinuation	No
Topical calcineurin inhibitors.		No
Topical and oral antihistamines (other than those allowed as background therapy).		No
Routine doses of doxepin (daily or every other day during 5 or more consecutive days).		No
LTRAs and H2 receptor antagonists, unless stable and taken for diseases other than CSU.		Yes for LTRAs; No for H2 receptor antagonists (SDG Leukotriene receptor antagonists for obstructive airway diseases Narrow)
Additional H1-AH up to 4-fold (2-fold in Japan)	No IMP discontinuation	No
Corticosteroids		Yes (SDG Corticosteroids Narrow excluding where Route is Topical, Nasal, Respiratory (Inhalation) or Ophthalmic)

a When yes, if confirmed through blinded medical review the estimand for the intercurrent event handling strategy will be as follows: hypothetical for continuous endpoints, and composite for responder and time-to-event endpoints. When no, a treatment policy strategy will be applied.

The primary efficacy endpoints were analyzed using an analysis of covariance (ANCOVA) model with the baseline value of the primary endpoint, intervention group, presence of angioedema at baseline, and region as covariates, with intercurrent events and missing data being handled by a hybrid method of the worst-observation carried forward (WOCF) and multiple imputation. Descriptive statistics including number of participants, mean, standard error, and least squares (LS) means was provided. In addition, difference in LS means and the corresponding 95% confidence intervals (CI) was provided along with the p-values.

Intercurrent events and corresponding strategy:

- *Prohibited medications and/or rescue medications*: For participants taking selected prohibited medications and/or rescue medications, their data after the medication start date were set to missing, and the worst postbaseline value on or before the time of the medication usage was

used to impute missing Week 24 value (for participants whose postbaseline values were all missing, the baseline was used to impute).

- *Discontinuation of study treatment:*

  Participants who discontinued the intervention prematurely were encouraged to follow the planned clinical visits and in these participants, who did not take the selected prohibited medications and/or rescue medications, all data collected after intervention discontinuation was used in the analysis. For these participants, missing data may still happen despite all efforts to collect the data after intervention discontinuation.

  - Lack of efficacy: For participants who discontinued study intervention due to lack of efficacy, all data collected after discontinuation was used in the analysis, and a WOCF approach was used to impute missing Week 24 value if needed (ie due to study discontinuation).
  - Other reasons: For participants who discontinued study intervention not due to lack of efficacy, a multiple imputation approach was used to impute missing Week 24 value. This multiple imputation used all participants excluding participants who had taken the selected prohibited medications and/or rescue medications on or before Week 24 and excluding participants who discontinued due to lack of efficacy on or before Week 24. Each of the imputed complete data was analyzed by fitting an ANCOVA model as described above. Statistical inference obtained from all imputed data was combined using Rubin's rule.

The secondary estimands largely correspond to the primary estimands.

Supplementary Analysis for Primary Endpoint

The following sensitivity analyses were performed targeting the same estimand as the primary estimand to assess the impact of the missing data handling strategy.

1. Tipping point analysis on WOCF

A tipping point analysis was performed for the primary endpoint with imputed WOCF Week 24 values as follows:

- A positive amount *d* is added to the imputed WOCF values, with the resulting score not to exceed the worst possible score (ie, 42 on UAS7)
- Change from baseline in endpoint was analyzed using ANCOVA model same as the one in primary analysis. A multiple imputation was used for missing Week 24 data.

The above was repeated iteratively until the p-value for treatment effect of dupilumab compared to placebo estimated was >0.021 at IA or >0.043 at final analysis, or all participants with data imputed by WOCF were assigned the worst possible score.

2. Pattern mixture model with copy increment from placebo after WOCF

After using the WOCF approach to impute data after taking the select prohibited/rescue medications and to impute missing data for participants who discontinue treatment due to lack of efficacy (as described for the primary analysis) the primary endpoint was analyzed with imputed missing Week 24 values using a pattern mixture model with copy increment from placebo. This copy increment from placebo implies that when participants discontinue intervention early, they continue to take advantage of their previous therapy, but they progress in the same way as participants in the placebo group.

The imputed dataset was analyzed by fitting an ANCOVA model same as the one in primary analysis.

3. Pattern mixture model with copy increment from placebo without WOCF

All data after taking the select prohibited/rescue medications was set to missing. The primary endpoint was analyzed with imputed missing Week 24 values using a pattern mixture model with copy increment from placebo (described above).

4. Tipping point analysis for missing data

After using the WOCF approach to impute data after taking select prohibited/rescue medications and to impute missing data for participants who discontinued treatment due to lack of efficacy (as described for the primary analysis), a tipping point analysis was performed for the primary endpoint with imputed missing Week 24 values as follows:

- **Step 1.** Monotone missing pattern was induced by Markov Chain Monte Carlo (MCMC) method using PROC MI: for participants who had intermediate missing values, the intermediate missing values was imputed assuming a multivariate normal distribution over observations from all visits. 40 datasets with a monotone missing pattern was obtained using this method.
- **Step 2.** For each of the imputed dataset with monotone missing pattern obtained in Step 1, the remaining missing data was imputed using the regression method for the monotone pattern with adjustment for covariates including response variable, intervention groups, angioedema at baseline, region, and baseline value of the corresponding endpoint. All available data in the monotone missing pattern data was used. One imputed dataset was obtained for each of the imputed dataset at Step 1. So, 40 fully imputed datasets were obtained altogether.
- **Step 3.** The imputed values in dupilumab group were added by a positive amount *d* for each imputed data set.
- **Step 4.** The imputed values in placebo group were subtracted by a positive amount *p* for each imputed data set.
- **Step 5.** Change from baseline in endpoint was analyzed using ANCOVA model same as the one in primary analysis. Then the SAS MIANALYZE procedure was used to generate statistical inferences by combining results from the 40 analyses using Rubin's formula.

Step 3 to Step 5 was repeated iteratively until the p-value for treatment effect of dupilumab compared to placebo estimated in Step 5 was >0.021 at IA or >0.043 at final analysis. LS mean difference between dupilumab and placebo in change from baseline in primary endpoint at Week 24 and the corresponding p-values was provided for each combination of shift parameters.

The following supplementary analysis was performed:

- *As-observed analysis* (Including all data after taking selected prohibited and/or rescue medications):

  The data collected after taking the select prohibited medications and/or rescue medications was included in the sensitivity analysis to evaluate the robustness of the primary analysis results with respect to the intercurrent event handling strategy while taking selected prohibited medications and/or rescue medications (eg. treatment policy strategy). For missing data, a multiple imputation approach was used to impute missing Week 24 value, and this multiple imputation will use all participants.

- *Worst possible score*

  For participants taking selected prohibited and/or rescue medications, their data after the medication start date was excluded from the analysis, and the worst possible score (ie, 21 for ISS7 and 42 for UAS7) was assigned to the Week 24 value. In case there is missing data, a multiple imputation approach was used to impute missing Week 24 value, and this multiple imputation used all participants excluding participants who had taken the selected prohibited medications and/or rescue medications on or before Week 24. Each of the imputed complete data was analyzed by fitting an analysis of covariance (ANCOVA) model with the baseline value of the primary endpoint, intervention group, presence of angioedema at baseline, and region as covariates. Statistical inference obtained from all imputed data was combined using Rubin's rule.

Multiplicity

A multiplicity procedure was proposed to control the overall type-I error rate for testing the primary and selected secondary endpoints. The overall type-I error is controlled at 0.05. The alpha spending at the interim analysis was 0.021, and the alpha spending at the final analyses when all 108 patients completed the study was 0.043.

At the interim analysis, the comparisons with placebo was tested based on the hierarchical

order below at 2-sided alpha=0.021, at the final analysis based on the hierarchical order

below at 2-sided alpha=0.043.

The hierarchical order of the endpoints was defined as:

1. Change from baseline in UAS7 at Week 24
2. Change from baseline in ISS7 at Week 24
3. Change from baseline in HSS7 at Week 24
4. Proportion of patients with MID (ISS7 ≥5) response at Week 24
5. Proportion of patients with UAS7 ≤6 at Week 24
6. Proportion of patients with UAS7 = 0 at Week 24
7. Change from baseline in UCT at Week 24

Interim Analysis

An interim analysis (IA) was performed when the first 83 randomized participants would have completed their 24-week treatment period by the interim analysis cut-off date 17.12.2021. This interim analysis used the O'Brien-Fleming approach with information fraction 0.77 and overall type-I error controlled at 0.05, with an alpha spending at the interim analysis of 0.021, and an alpha spending at the final analysis (when all 108 patients complete the study) of 0.043.

The possible outcomes from this interim analysis are summarized in the Table 20 below:

Table 20. Possible outcomes from the interim analysis

UAS7 (treatment effect)	ISS7 (treatment effect)		
	≤0.021	p>0.021 and p≤0.1	p>0.1
≤0.021	Efficacy at IA for ISS7 and UAS7	Continue up to EOT for final analysis	Continue up to EOT for final analysis
p>0.021 and p≤0.1	Continue up to EOT for final analysis	Continue up to EOT for final analysis	Continue up to EOT for final analysis
p>0.1	Efficacy at IA for ISS7	Continue up to EOT for final analysis	Stop for futility

The primary analysis population for the efficacy endpoints was the ITT24 population for the interim analysis.

Subgroup Analyses

To assess the homogeneity of the treatment effect across various subgroups, analyses were performed on the primary endpoint across the following subgroups:

- Age group (<median, ≥median; <65, ≥65 years)
- Gender (Male, Female)
- Baseline weight (<median, ≥median, <60, ≥60 kg)
- Baseline BMI (<25, ≥25- <30, ≥30 kg/m2)
- Region
- Territory
- Race (White, all the Others)
- Ethnicity (Hispanic, non-Hispanic)
- Angioedema at baseline (Yes, No)
- Baseline UAS7 score (<28, ≥28)
- Baseline ISS7 score (<13, ≥13)
- Duration of disease (<2, 2-10, >10 years)
- H1-AH baseline dose (1-fold, 2-4-fold)
- Baseline Total serum IgE (<median, ≥median)

To assess the consistency of the treatment effects across the subgroup levels, subgroup analyses was conducted for the primary endpoint at Week 24. The analysis was performed based on imputed datasets from the primary analysis.

To test the interaction between intervention and subgroup factor, an ANCOVA model incorporating subgroup-by-treatment interaction was built for each subgroup factor. The model included all the covariates in the main statistical model plus the subgroup variable (if not one of the covariates adjusted in the main model already) and the subgroup-by-treatment interaction. Statistical inference obtained from all imputed data was combined using Rubin's rule. A p-value for the test of interaction was provided based on the combined inference.

In each subgroup, the primary endpoint was analyzed using the primary approach for the primary endpoint, but on the specific subgroup of the imputed primary analysis population.

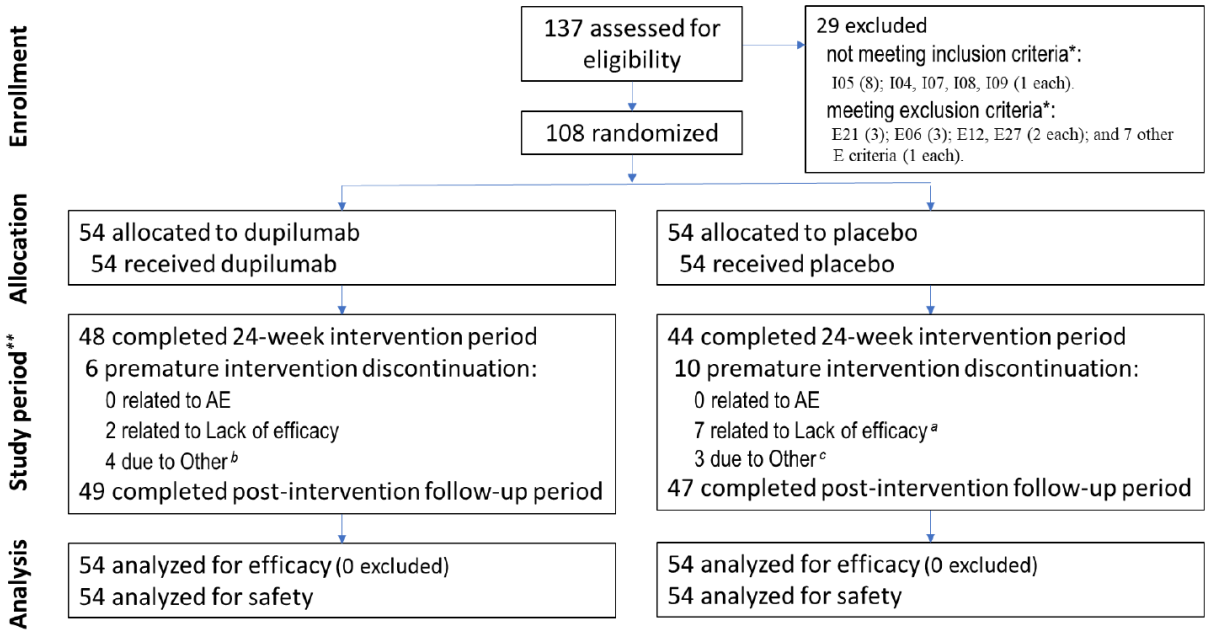
2.4.2.2. Results

Participant flow

A total of 108 participants (including 2 adolescents) were randomized to intervention (54 in the dupilumab group and 54 in the placebo group) comprising the ITT population. All randomized participants were treated. 29 participants were screened but not randomized (screen failures). The most frequent reason for screen failure was not meeting inclusion criterion I05 (UAS7 ≥16 and ISS7 ≥8 during 7 days before randomization).

Early intervention discontinuation occurred in 6 participants (11.1%) in the dupilumab group and in 10 (18.5%) participants in the placebo group, respectively. Of these, 6 participants (1 in the dupilumab group and 5 in the placebo group) completed the follow-up period of the study, while the other 10 participants (5 in each group) did not complete the follow-up period and prematurely discontinued the study (including 1 lost to follow-up in the placebo group). A total of 92 (85.2%) participants completed the study intervention period. Two participants (both in the placebo group) did not complete the follow-up period and prematurely discontinued the study.

Figure 25. Patient Disposition EFC16461 Study B



Source: Table 6 and Appendix 16.2.1 Participant disposition, Tables 16.2.1.1, 16.2.1.3, 16.2.1.5, 16.2.1.6.
* Refer to Appendix 16.1.1 Protocol for definitions of inclusion and exclusion criteria.
** Study period = study intervention period + post-intervention follow-up period.
a Including 2 Withdrawal by subject due to lack of efficacy.
b 3 Withdrawal by subject due to other reasons (other than lack of efficacy or AE) and 1 per Sponsor decision after IA.
c 1 Poor compliance to protocol, 1 Withdrawal by subject due to other reason (other than lack of efficacy or AE), and 1 per Sponsor decision after IA.

Recruitment

EFC16461 Study B

First participant enrolled: 03 March 2020

Last participant visit:	23 June 2022
The primary analysis data cut-off:	18 July 2022

Conduct of the study

Protocol amendments (related to Study B)

The original master protocol dated 24 October 2019 was modified per 3 global amendments (amendment 02 dated 30 April 2020, amendment 04 dated 29 April 2021, amendment 05 dated 17 March 2022) and 2 local amendments (amendment 01 for Japan dated 10 February 2020, amendment 03 for France dated 09 October 2020).

Amendment 02 included a switch of the primary and the key secondary endpoints to establish the weekly urticaria activity score (UAS7) as the primary endpoint for European Union (EU) and EU reference countries based on recommendations from European Medicines Agency (EMA). Amendment 04 introduced an interim analysis for Study B after 80 randomized participants completed their 24-week treatment period. Amendment 05 was not applicable to Study B.

COVID-19 pandemic

EFC16461 Study B was conducted during the global COVID-19 pandemic which began in March 2020. The study began in February 2020 and continued without stoppage during the global COVID-19 pandemic.

In response to the global COVID-19 pandemic, contingency measures in study conduct were introduced in amendment 02, which allowed implementation of temporary or alternative mechanisms such as phone contact, virtual visits, online meetings, use of local clinic or laboratory locations, and home visits by skilled staff (as permitted per local regulation) to ensure the study continuity and protect participants' safety. No waivers to deviate from protocol enrollment criteria due to COVID-19 were granted. Remote monitoring was implemented when on-site monitoring was not allowed. All temporary mechanisms utilized and deviations from planned study procedures were documented as being related to the COVID-19 pandemic.

Interim analysis (protocol amendment 04)

An interim analysis (IA) of Study B was introduced via protocol amendment 04 to allow an earlier declaration of efficacy, continuation of the study, or study stop for futility (see "Statistical methods; 5.4.2.1)). The proposed IA was to be conducted when the first 80 randomized participants (out of 104 planned) would have completed their 24-week treatment period by the IA cut-off date (17 Dec 2021). To maintain the study integrity following the IA with respect to subsequent study conduct and/or data analyses, a dissemination plan was prepared prior to IA database lock to clearly define and set up two separate study teams (blinded and unblinded), an independent-to-Sponsor statistical group, and an independent-to-Sponsor Interim Analysis Review Committee (IARC). The independent-to-Sponsor statistical group (WCG/ACI Clinical Services, Bala Cynwyd, PA, USA) was responsible for performing the interim efficacy analysis and providing the results to the IARC. The IARC was composed of 2 external experts (one statistician and one clinician) who were independent of Sponsor and without any involvement in the EFC16461 studies.

The results of the interim analysis (see 5.4.2.2.1) met the protocol specified efficacy statistical criteria for futility and the Sponsor sent a notification to Investigators and sites on 18 February 2022 with instructions that the Investigators were to contact and inform participants who were still receiving study treatment and organize an early end-of-treatment visit. A public disclosure (press release) of interim analysis futility was issued on the same day (18 February 2022).

Given the status of the 25 participants not included in the interim analysis, the Sponsor decided to maintain the study integrity following the interim analysis with respect to subsequent study conduct and/or data analyses and conduct a final analysis after the conclusion of Study B when all randomized participants (ITT population) had completed their last study visit.

At the time of the interim analysis, the recruitment target had been met and recruitment had been closed at 108 randomized participants. The status of the 25 participants not included in the interim analysis (ITT24 population) at and/or after the public disclosure of futility (18 February 2022) was as follows:

- 1 participant had discontinued treatment.
- 9 participants had completed their scheduled end-of-treatment visit.
- 12 participants were scheduled to complete their end-of-treatment visit within 1 month of public disclosure of futility and completed study treatment period.
- 3 participants discontinued study intervention (2 due to Sponsor Notification and 1 due to lack of efficacy).

Protocol deviations

Major protocol deviations were reported in 24 participants overall, evenly distributed between the two intervention groups (12 [22.2%] participants in each group). The most frequently reported major protocol deviations were in the categories "Inclusion/Exclusion criteria" (7 [13.0%] participants in the dupilumab group and 5 [9.3%] in the placebo group) and "Concomitant medications/therapy" (2 [3.7%] in the dupilumab group and 5 [9.3%] in the placebo group). There were no deviations assessed as critical in the study.

In the "Inclusion/exclusion criteria category", 7 participants had deviations related to not meeting inclusion criteria I 04 (all due to not meeting "stable H1-antihistamine dose for at least 3 consecutive days prior to the screening"). 3 participants had deviations related to exclusion criteria E 17 "omalizumab treatment taken within 4 months before screening." The 3 participants signed informed consent less than 4 months after the last omalizumab treatment, but all 3 participants were randomized more than 4 months after the last omalizumab treatment. 1 participant in the dupilumab group had a deviation related to not meeting inclusion criteria I 05 "During the 7 days before randomization: UAS7≥16 and ISS7 ≥8" due to missing 1 day of e-Diary entry in the 7 days before randomization.

7 participants had deviations in the "Concomitant medications/therapy" category, all related to background H1-antihistamines not administered as per protocol (1 participant discontinued H1-AH after Week 14 per Investigator's decision for lack of efficacy, 2 participants had missing H1-AH doses for more than 7 days, 3 participants had missing H1-AH doses for 3 to 7 days, and 1 participant had an incident of taking 5-fold of standard H1-AH dose).

Breaking of the blind

For the purpose of interim analysis, the blind was broken for the independent IARC and for the predefined unblinded team according to the dissemination plan. Post IA, the study was conducted by the blinded study team and proceeded to early EOT visit for all ongoing participants, as appropriate.

Baseline data

Demographics

The mean (SD) age of the participants was 47.7 (15.9) years with a range of 14 to 79 years, 72.2% were females, and the majority of participants (77.8%) were White. There were 106 (98.1%) adults and 2 (1.9%) adolescents (≥12 to <18 years) randomized in the study. The mean body weight was 77.68 kg, with 21 (19.4%) of participants <60 kg and 87 (80.6%) participants ≥60 kg (Table 23). Two adolescents, one per each treatment group, were included in the study. There were no participants with body weight <30 kg as per protocol defined exclusion criteria.

Table 21. Demographics and participant characteristics at baseline - Randomized population – EFC16461 Study B

	Placebo (N=54)	Dupilumab (N=54)	All (N=108)
Age (years)			
Number	54	54	108
Mean (SD)	46.8 (16.3)	48.6 (15.6)	47.7 (15.9)
Median	48.5	49.0	49.0
Q1 ; Q3	33.0 ; 59.0	41.0 ; 56.0	36.0 ; 58.5
Min ; Max	16 ; 77	14 ; 79	14 ; 79
Age group (years) [n (%)]			
Number	54	54	108
12-17	1 (1.9)	1 (1.9)	2 (1.9)
18-39	18 (33.3)	12 (22.2)	30 (27.8)
40-64	27 (50.0)	31 (57.4)	58 (53.7)
65-74	6 (11.1)	8 (14.8)	14 (13.0)
≥75	2 (3.7)	2 (3.7)	4 (3.7)
Region[a] [n (%)]			
Number	54	54	108
Asia	7 (13.0)	6 (11.1)	13 (12.0)
Latin America	7 (13.0)	8 (14.8)	15 (13.9)
East Europe	11 (20.4)	11 (20.4)	22 (20.4)
Western Countries	29 (53.7)	29 (53.7)	58 (53.7)
Territory[b] n (%)]			
Number	54	54	108
North America	16 (29.6)	18 (33.3)	34 (31.5)
European Union & United Kingdom	15 (27.8)	13 (24.1)	28 (25.9)
Rest of World	23 (42.6)	23 (42.6)	46 (42.6)
Sex [n (%)]			
Number	54	54	108
Male	13 (24.1)	17 (31.5)	30 (27.8)
Female	41 (75.9)	37 (68.5)	78 (72.2)
Race [n (%)]			
Number	54	54	108
White	41 (75.9)	43 (79.6)	84 (77.8)
Black or African American	2 (3.7)	3 (5.6)	5 (4.6)
Asian	11 (20.4)	6 (11.1)	17 (15.7)
Japanese	7 (13.0)	6 (11.1)	13 (12.0)
Native Hawaiian or Other Pacific Islander	0	1 (1.9)	1 (0.9)
American Indian or Alaska Native	0	0	0
Multiple	0	0	0
Not reported	0	1 (1.9)	1 (0.9)
Unknown	0	0	0

	Placebo (N=54)	Dupilumab (N=54)	All (N=108)
Ethnicity [n (%)]			
Number	54	54	108
Hispanic or Latino	7 (13.0)	7 (13.0)	14 (13.0)
Not Hispanic or Latino	46 (85.2)	47 (87.0)	93 (86.1)
Not reported	1 (1.9)	0	1 (0.9)
Weight (kg)			
Number	54	54	108
Mean (SD)	75.26 (18.37)	80.10 (17.70)	77.68 (18.12)
Median	73.65	79.60	77.00
Q1 ; Q3	59.50 ; 87.00	68.10 ; 93.00	61.40 ; 90.00
Min ; Max	36.6 ; 114.1	49.0 ; 135.0	36.6 ; 135.0
Weight group (kg) [n (%)]			
Number	54	54	108
<60	14 (25.9)	7 (13.0)	21 (19.4)
≥60	40 (74.1)	47 (87.0)	87 (80.6)
BMI (kg/m^2)			
Number	54	54	108
Mean (SD)	27.27 (5.68)	28.57 (6.25)	27.92 (5.98)
Median	26.37	28.22	27.44
Q1 ; Q3	22.72 ; 30.86	24.16 ; 32.54	23.30 ; 31.94
Min ; Max	14.3 ; 44.5	17.6 ; 47.3	14.3 ; 47.3
BMI group (kg/m^2) [n (%)]			
Number	54	54	108
<30	34 (63.0)	33 (61.1)	67 (62.0)
≥30	20 (37.0)	21 (38.9)	41 (38.0)

BMI: Body mass index

a Asia: China and Japan; Latin America: Argentina; East Europe: Russia, Hungary; Western Countries: Canada, USA, France, Germany, Spain, United Kingdom;

b North America: Canada, USA; European Union & United Kingdom: France, Germany, Hungary, Spain, United Kingdom; Rest of World: China, Japan, Argentina, Russia

PGM=PRODOPS/SAR231893/EFC16461/CSR_B4/REPORT/PGM/dem_demo_r_t.sas
OUT=REPORT/OUTPUT/dem_demo_r_t_i.rtf (08AUG2022 5:03)

Baseline disease characteristics

The mean (SD) age at onset of CSU was 39.1 (17.1) years. The mean (SD) time since first diagnosis of CSU prior to study entry was 9.1 (9.0) years; 98.1% of participants had more than 1 year of disease duration prior to study participation. The mean (SD) ISS7 and UAS7 scores at baseline were 16.0 (3.9) and 31.5 (8.0), respectively, indicative of severe itch and urticaria activity at baseline for the enrolled participants. Per protocol, all participants had at least moderate urticaria activity (UAS7 score =16 to 27 at baseline) with the vast majority of participants (69.4%) with severe urticaria activity (UAS7 score of ≥28 at baseline). A total of 53 (49.1%) participants presented with angioedema at baseline (AAS7 >0). At baseline, there were 104 (96.3%) participants who were incomplete responders to omalizumab and 4 (3.7%) participants who were intolerant to omalizumab, with 56.5% of participants previously treated with omalizumab for ≥6 months. The majority (81.5%) of participants had previous exposure to the approved omalizumab 300 mg q4w dose regimen and 3.8% of participants had a dose regimen higher than the highest approved dose of 300 mg. All participants were receiving H1-antihistamines for CSU (including 1 participant in the placebo group whose baseline H1-

antihistamine treatment was confirmed after database lock), with 36.4% on standard approved dose, 38.3% on 2- to 3-fold of standard dose, and 25.2% on 4-fold of standard dose. The mean total IgE at baseline was 223.2 IU/mL and the median total IgE at baseline was 77.0 IU/mL.

Table 22. Disease characteristics at baseline - Randomized population – EFC16461 Study B

	Placebo (N=54)	Dupilumab (N=54)	All (N=108)
Age at onset of CSU (years)			
Number	54	54	108
Mean (SD)	37.3 (18.0)	40.9 (16.1)	39.1 (17.1)
Median	34.0	43.0	40.5
Q1 ; Q3	24.0 ; 52.0	33.0 ; 51.0	25.5 ; 51.5
Min ; Max	2 ; 76	6 ; 72	2 ; 76
Time since first diagnosis of CSU (years)			
Number	54	54	108
Mean (SD)	9.9 (10.1)	8.3 (7.8)	9.1 (9.0)
Median	7.0	6.2	6.6
Q1 ; Q3	2.8 ; 15.0	2.7 ; 10.0	2.7 ; 12.5
Min ; Max	1 ; 53	1 ; 37	1 ; 53
Baseline ISS7 score			
Number	54	54	108
Mean (SD)	16.2 (3.8)	15.9 (4.0)	16.0 (3.9)
Median	16.0	16.0	16.0
Q1 ; Q3	13.0 ; 21.0	13.0 ; 20.0	13.0 ; 20.0
Min ; Max	8 ; 21	8 ; 21	8 ; 21
Baseline ISS7 score [n (%)]			
Number	54	54	108
<13	9 (16.7)	13 (24.1)	22 (20.4)
≥13	45 (83.3)	41 (75.9)	86 (79.6)
Baseline UAS7 score			
Number	54	54	108
Mean (SD)	31.9 (8.1)	31.0 (7.9)	31.5 (8.0)
Median	31.5	31.5	31.5
Q1 ; Q3	26.0 ; 40.0	24.0 ; 37.0	25.5 ; 38.5
Min ; Max	16 ; 42	16 ; 42	16 ; 42
Baseline UAS7 score [n (%)]			
Number	54	54	108
<28	18 (33.3)	15 (27.8)	33 (30.6)
≥28	36 (66.7)	39 (72.2)	75 (69.4)
Baseline HSS7 score			
Number	54	54	108
Mean (SD)	15.7 (5.0)	15.1 (4.7)	15.4 (4.8)
Median	16.5	16.0	16.0
Q1 ; Q3	12.0 ; 21.0	12.0 ; 19.0	12.0 ; 20.5
Min ; Max	4 ; 21	6 ; 21	4 ; 21
Presence of angioedema at baseline[a] [n (%)]			
Number	54	54	108
Yes	33 (61.1)	20 (37.0)	53 (49.1)
No	21 (38.9)	34 (63.0)	55 (50.9)

	Placebo (N=54)	Dupilumab (N=54)	All (N=108)
Baseline AAS7 score for participants with angioedema[a]			
Number	33	20	53
Mean (SD)	42.9 (24.9)	38.0 (27.4)	41.1 (25.8)
Median	40.0	32.0	40.0
Q1 ; Q3	23.0 ; 62.0	16.5 ; 62.0	17.0 ; 62.0
Min ; Max	7 ; 104	4 ; 85	4 ; 104
Baseline UCT score			
Number	53	53	106
Mean (SD)	4.1 (2.9)	4.5 (3.2)	4.3 (3.1)
Median	4.0	4.0	4.0
Q1 ; Q3	2.0 ; 6.0	2.0 ; 7.0	2.0 ; 6.0
Min ; Max	0 ; 11	0 ; 11	0 ; 11
Baseline DLQI score[b]			
Number	51	49	100
Mean (SD)	13.8 (7.2)	13.1 (7.0)	13.5 (7.1)
Median	15.0	12.0	13.0
Q1 ; Q3	7.0 ; 19.0	8.0 ; 20.0	8.0 ; 19.0
Min ; Max	2 ; 30	1 ; 28	1 ; 30
Baseline CU-Q2oL score			
Number	53	53	106
Mean (SD)	44.4 (20.7)	42.7 (20.0)	43.6 (20.3)
Median	44.6	40.2	43.5
Q1 ; Q3	29.3 ; 54.3	26.1 ; 58.7	27.2 ; 58.7
Min ; Max	5 ; 93	9 ; 86	5 ; 93
Baseline PGIS score			
Number	54	54	108
Mean (SD)	3.4 (0.7)	3.4 (0.6)	3.4 (0.7)
Median	3.5	3.0	3.0
Q1 ; Q3	3.0 ; 4.0	3.0 ; 4.0	3.0 ; 4.0
Min ; Max	2 ; 4	1 ; 4	1 ; 4
Baseline Total IgE (IU/mL)			
Number	52	52	104
Mean (SD)	182.9 (322.6)	263.5 (688.5)	223.2 (536.5)
Median	85.8	72.1	77.0
Q1 ; Q3	22.2 ; 204.5	19.2 ; 216.5	20.0 ; 204.5
Min ; Max	1 ; 1595	1 ; 4699	1 ; 4699
Baseline Total IgE (IU/mL) [n (%)]			
Number	52	52	104
<50	22 (42.3)	24 (46.2)	46 (44.2)
≥50	30 (57.7)	28 (53.8)	58 (55.8)
Baseline H1-antihistamines [n (%)]			
Number	53	54	107
standard dose	18 (34.0)	21 (38.9)	39 (36.4)
2-3-fold standard dose	22 (41.5)	19 (35.2)	41 (38.3)
4-fold standard dose	13 (24.5)	14 (25.9)	27 (25.2)

	Placebo (N=54)	Dupilumab (N=54)	All (N=108)
Incomplete response to Omalizumab vs Intolerant to Omalizumab [n (%)]			
Number	54	54	108
Incomplete responder	50 (92.6)	54 (100)	104 (96.3)
Intolerant	4 (7.4)	0	4 (3.7)
Duration of prior Omalizumab treatment [n (%)]			
Number	54	54	108
<6 months	25 (46.3)	22 (40.7)	47 (43.5)
6-12 months	14 (25.9)	13 (24.1)	27 (25.0)
>12 months	15 (27.8)	19 (35.2)	34 (31.5)
Time from the last Omalizumab intake to randomization			
Number	54	54	108
Mean (SD)	17.9 (18.1)	15.2 (15.4)	16.6 (16.8)
Median	10.3	7.6	9.3
Q1 ; Q3	6.0 ; 18.8	6.0 ; 17.4	6.0 ; 18.1
Min ; Max	5 ; 85	4 ; 63	4 ; 85
Last dose of Omalizumab prior to study[c]			
Number	54	54	108
300 mg q2w	6 (11.1)	9 (16.7)	15 (13.9)
150 mg q2w	0	1 (1.9)	1 (0.9)
600 mg q4w	0	2 (3.7)	2 (1.9)
450 mg q4w	1 (1.9)	1 (1.9)	2 (1.9)
300 mg q4w	47 (87.0)	41 (75.9)	88 (81.5)

ISS7: itch-severity score over 7 days (0-21); UAS7: urticaria activity score over 7 days (0-42); HSS7: hives-severity score over 7 days (0-21); AAS7: angioedema activity score over 7 days (0-105); UCT: urticaria control test (0-16); DLQI: Dermatology Quality of Life (0-30); PGIS: Patient Global Impression of Severity (1-4); CU-Q2oL: chronic urticaria quality of life questionnaire (0-100)

a Participants with an AAS7 baseline score > 0

b Excludes 1 adolescent who completed the CDLQI and 5 adults who incorrectly completed the CDLQI.

c Xolair USPI doses/regimen for CIU (CSU): XOLAIR 150 or 300 mg SC every 4 weeks.

PGM=PRODOPS/SAR231893/EFC16461/CSR_B4/REPORT/PGM/dem_disease_r_t.sas
OUT=REPORT/OUTPUT/dem_disease_intext_r_t_i.rtf (13OCT2022 10:35)

Medical history and concurrent illnesses

The most common predefined medical history was angioedema, reported in 64.8% of participants overall. Other common predefined medical histories (in >10% of participants overall) included asthma (19.4%) and allergic rhinitis (17.6%). One participant in the placebo group had active AD at study entry which was an exclusion criterion and was reported as a minor protocol deviation; 5.6% of participants had previous history of AD overall.

Additionally, 12 (11.1%) participants had a medical history of at least 1 CSU-associated autoimmune disorder: autoimmune thyroid disease in 8 (7.4%) participants (4 with autoimmune thyroiditis and 4 with Basedow's [or Grave's] disease) and vitiligo in 4 (3.7%) participants.

Prior and concomitant medications

The prior medications used for CSU, including H1-antihistamines and oral corticosteroids (OCS), were balanced between intervention groups. The most commonly used H1-antihistamine was cetirizine/cetirizine hydrochloride (46.3%), and the most commonly used OCS was prednisolone

(12.0%). The majority of participants (70.4%) reported the use of prior medications within 1 month of screening for reasons other than CSU ([16.2.4.3.3] and [16.2.4.3.4]). The most frequently used prior medications for reasons other than CSU (in >5% of participants) included levothyroxine sodium/levothyroxine (13.9%), paracetamol (10.2%), amlodipine besilate (6.5%), and salbutamol (5.6%).

All patients received background antihistamine treatment that had to remain stable throughout the study. At baseline, all participants were receiving H1-antihistamines for CSU, with 36.4% on standard dose and 63.6% on 2- to 4-fold of standard dose. OCS as concomitant medication (any purpose) was reported for 8 (14.8%) participants in the dupilumab group and 11 (20.4%) in the placebo group with prednisolone and prednisone being the most common. The 3 most frequently used concomitant medications other than H1-antihistamine or OCS included paracetamol (11.1% in the dupilumab group and 14.8% in the placebo group), levothyroxine sodium (13.0% and 5.6%, respectively), and salbutamol (9.3% and 1.9%, respectively).

Numbers analysed

All randomized participants (n= 108; 54 in each intervention group) were included in the final efficacy population (ITT population). For the interim analysis (IA), the ITT24 population (n=83; 43 in the dupilumab group and 40 in the placebo group) was analysed.

2.4.2.2.1. Outcomes and estimation

A summary of results for the primary and secondary endpoints in study B is provided below.

Table 23. Summary of the primary and secondary endpoints in the hierarchical testing procedure - ITT population – EFC16461 Study B

Parameter	Placebo [a] (N=54)	Dupilumab [a] (N=54)	Difference (95% CI) [b] for Dupilumab vs. Placebo	P-value [c]
Primary endpoint				
Change from baseline in UAS7 at Week 24	-8.54 (2.14)	-14.37 (2.16)	-5.83 (-11.37, -0.30)	**0.0390**
Secondary endpoints				
Change from baseline in ISS7 at Week 24	-4.81 (1.08)	-7.68 (1.10)	-2.87 (-5.68, -0.07)	0.0449
Change from baseline in HSS7 at Week 24	-3.63 (1.11)	-6.64 (1.11)	-3.01 (-5.88, -0.14)	0.0397
Proportion of participants with MID (ISS7 ≥ 5) response at Week 24	21 (38.9)	32 (59.3)	1.987 (0.835, 4.729)	0.1203
Proportion of participants with UAS7 ≤ 6 at Week 24	10 (18.5)	13 (24.1)	1.899 (0.577, 6.247)	0.3107
Proportion of participants with UAS7 = 0 at Week 24	5 (9.3)	7 (13.0)	1.180 (0.268, 5.201)	0.8373
Change from baseline in UCT at Week 24	3.38 (0.74)	5.33 (0.77)	1.94 (-0.03, 3.92)	0.0534

CMH: Cochran-Mantel Haenszel; ISS7: itch-severity score over 7 days (0-21); UAS7: urticaria activity score over 7 days (0-42); HSS7: hives-severity score over 7 days (0-21); UCT: urticaria control test (0-16)

a Values presented are LS mean change from baseline for continuous variables and number and percent of responders for binary variables

b Difference is LS mean difference for continuous variables and CMH odds ratio for binary variables

c All values in bold font are statistically significant according to the hierarchical testing procedure

PGM=PRODOPS/SAR231893/EFC16461/CSR_B4/REPORT/PGM/eff_hierarchy_test_eu_i_t.sas
OUT=REPORT/OUTPUT/eff_hierarchy_test_eu_i_t_i.rtf (16AUG2022 9:28)

Primary efficacy endpoint

Change from baseline in UAS7 at Week 24

Baseline mean UAS7 was 30.99 and 31.93 in the dupilumab and placebo groups. The LS mean (SE) decrease from baseline in UAS7 at Week 24 was -14.37 (2.16) in the dupilumab group versus -8.54 (2.14) in the placebo group. The LS mean difference versus placebo (95% CI) was -5.83 (-11.37, -0.30); p=0.0390; SAP-specified threshold p<0.043). In the dupilumab group, the median UAS7 improved to a mild urticaria activity score of 14.00 (<16, in comparison, to 28.00 in the placebo group.

Table 24. Change from baseline in UAS7 at Week 24 - ITT population – EFC16461 Study B

UAS7	Placebo (N=54)	Dupilumab (N=54)
Baseline		
Number	54	54
Mean (SD)	31.93 (8.09)	30.99 (7.89)
Median	31.50	31.50
Q1 ; Q3	26.00 ; 40.00	24.00 ; 37.00
Min ; Max	16.0 ; 42.0	16.0 ; 42.0
Week 24		
Number	48	51
Mean (SD)	23.91 (14.98)	16.56 (13.34)
Median	28.00	14.00
Q1 ; Q3	12.30 ; 38.00	6.00 ; 24.00
Min ; Max	0.0 ; 42.0	0.0 ; 42.0
Change from baseline		
Number (observed/imputed)	48 (36/12)	51 (43/8)
Mean (SD)	-8.78 (14.80)	-14.21 (14.87)
Median	-2.50	-14.00
Q1 ; Q3	-21.20 ; 0.13	-27.17 ; -2.00
Min ; Max	-42.0 ; 19.8	-42.0 ; 13.0
LS Mean (SE)[a]	-8.54 (2.14)	-14.37 (2.16)
LS Mean Diff vs. placebo (95% CI)[a]		-5.83 (-11.37, -0.30)
P-value vs. placebo[a]		0.0390

WOCF: Worst observation carried forward; MI: Multiple imputation

a Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, presence of angioedema at baseline, and regions as covariates.

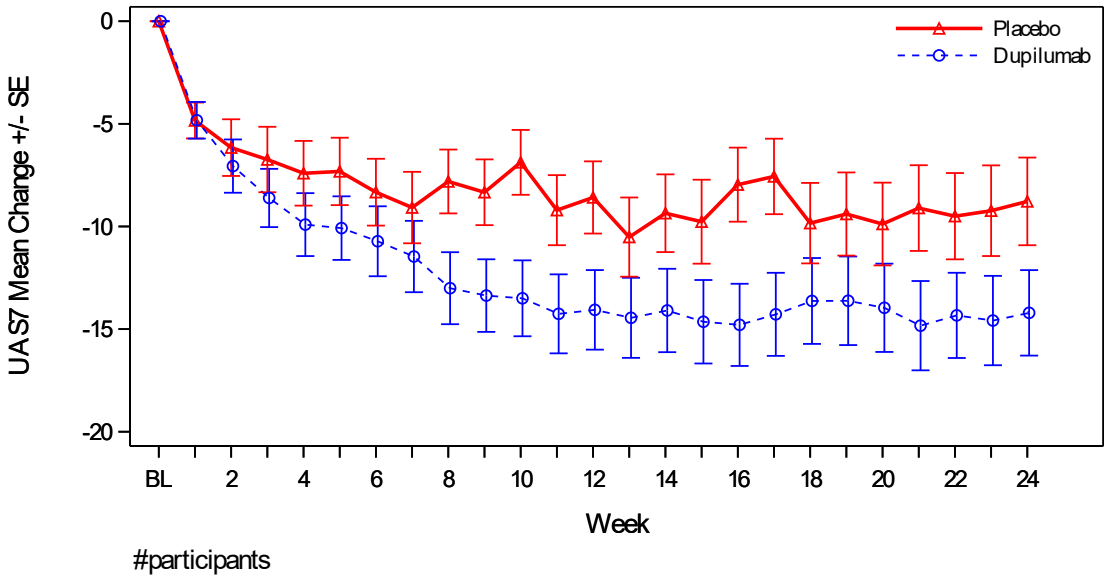
Note: Data collected after study intervention discontinuation were included. Data post select prohibited/rescue medications were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF; other missing data were imputed by MI. Descriptive statistics at Week 24 include participants after WOCF at Week 24, and participants whose values were imputed by MI at Week 24 were excluded from the descriptive analysis.

PGM=PRODOPS/SAR231893/EFC16461/CSR_B4/REPORT/PGM/eff_ancova_i_t.sas
OUT=REPORT/OUTPUT/eff_ancova_uas7_wk24_i_t_i.rtf (16AUG2022 8:59)

Dupilumab treatment led to a reduction over time in mean UAS7 through the 24-week treatment period. Early numerical improvements were observed between dupilumab and placebo with favorable numerical differences through Week 24. The LS mean (SE) change from baseline was -13.33 (1.94) in

the dupilumab group and -8.22 (1.91) in the placebo group with a LS mean difference of -5.11 (95%CI: -10.08, -0.13; nominal p= 0.0443).

Figure 26. Plot of mean change from baseline in UAS7 over time during the 24-week treatment period - ITT population – EFC16461 Study B



#participants

Placebo	54	54	54	53	50	53	53	51	50	51	49	47	48
Dupilumab	54	54	54	53	52	53	52	50	51	49	50	51	51

Supportive analyses

Sensitivity analyses

Consistent positive numerical difference of dupilumab treatment versus placebo in UAS7 reduction at Week 24 was also seen in the following sensitivity analyses:

- PMM with copy increment from placebo after WOCF: LS mean difference versus placebo (95% CI) = -5.64 (-11.09, -0.19); nominal p = 0.0425
- PMM with copy increment from placebo without WOCF: LS mean difference versus placebo (95% CI) = -5.52 (-10.93, -0.10); nominal p = 0.0459 ([16.2.6.1.4.3]).

Modified primary analyses censoring the data after the interim analysis futility notification

An additional analysis censoring the data after the interim analysis futility notification to Investigators and sites/public disclosure supported the positive numerical difference of dupilumab treatment versus placebo in UAS7 reduction at Week 24, with a LS mean difference versus placebo of -6.36 (95% CI: -12.20, -0.51; p=0.0330).

Proportion of participants with UAS7 ≤6 at Week 24

The proportion of participants with their CSU symptoms well controlled (UAS7 ≤6) was 24.1% in the dupilumab group and 18.5% in the placebo group at Week 24 (OR: 1.899, 95% CI: 0.577, 6.247, nominal p=0.3107) (Table 27).

Proportion of participants with UAS7=0 at Week 24 The proportion of participants with complete resolution of their CSU symptoms (UAS7=0) was 13.0% in the dupilumab group and 9.3% in the placebo group at Week 24 (OR: 1.180, 95% CI: 0.268, 5.201, nominal p=0.8373).

Post-hoc categorical improvement in urticaria activity severity from baseline

In the dupilumab group with severe urticaria activity at baseline, most of the participants, 73.0% (27 out of 37) had a reduced urticaria activity at Week 24. Of them, 13.5% achieved complete resolution of symptoms (defined as UAS7=0). In comparison, for participants in the placebo group with severe urticaria activity at baseline, 39.4% (13 out of 33) had a reduced urticaria activity at Week 24 with 9.1% achieving complete resolution.

Table 25. Shift table of UAS7 scores from baseline to Week 24 - ITT population– EFC16461 Study B

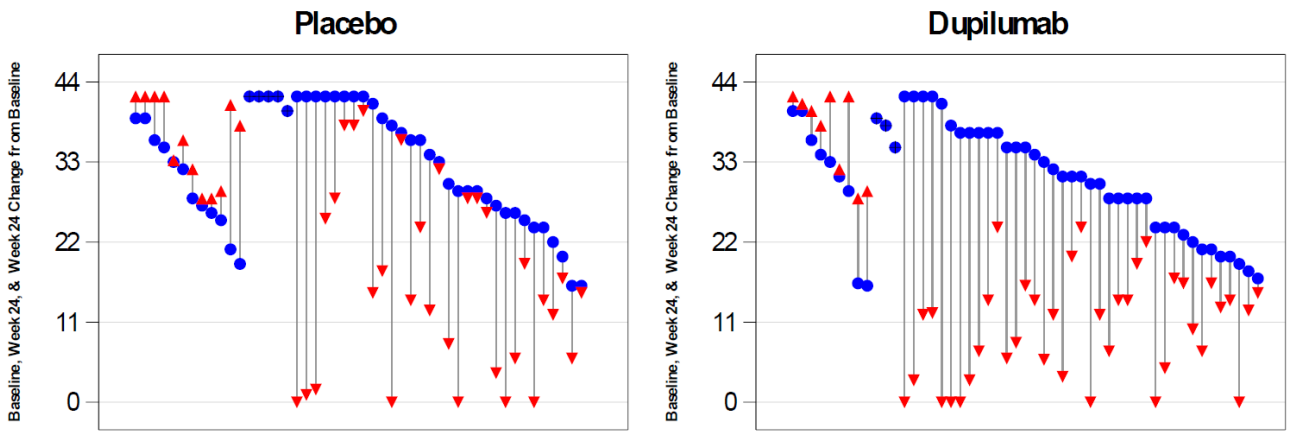
Baseline UAS7 score	Week 24 UAS7 score	Placebo (N=54)	Dupilumab (N=54)
Moderate (≥16 and <28) (N=33)	Complete/Well-Controlled (≤6)	5/15 (33.3)	3/14 (21.4)
	Complete Control (0)	2/15 (13.3)	2/14 (14.3)
	Well-Controlled (>0 and ≤6)	3/15 (20.0)	1/14 (7.1)
	Mild (>6 and <16)	3/15 (20.0)	6/14 (42.9)
	Moderate (≥16 and <28)	2/15 (13.3)	3/14 (21.4)
	Severe (≥28)	5/15 (33.3)	2/14 (14.3)
Severe (≥28) (N=75)	Complete/Well-Controlled (≤6)	5/33 (15.2)	10/37 (27.0)
	Complete Control (0)	3/33 (9.1)	5/37 (13.5)
	Well-Controlled (>0 and ≤6)	2/33 (6.1)	5/37 (13.5)
	Mild (>6 and <16)	4/33 (12.1)	11/37 (29.7)
	Moderate (≥16 and <28)	4/33 (12.1)	6/37 (16.2)
	Severe (≥28)	20/33 (60.6)	10/37 (27.0)

WOCF: Worst observation carried forward

Note: Data collected after study intervention discontinuation were included. Data post select prohibited/rescue medications were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF.

PGM=PRODOPS/SAR231893/EFC16461/CSR_B4/EXPLO/PGM/a_eff_shift_uas7_i_t.sas
OUT=EXPLO/OUTPUT/a_eff_shift_uas7_wk24_i_t_i.rtf (18AUG2022 11:44)

Figure 27. Waterfall plot of UAS7 at Week 24 by treatment group - ITT population – EFC16461 Study B

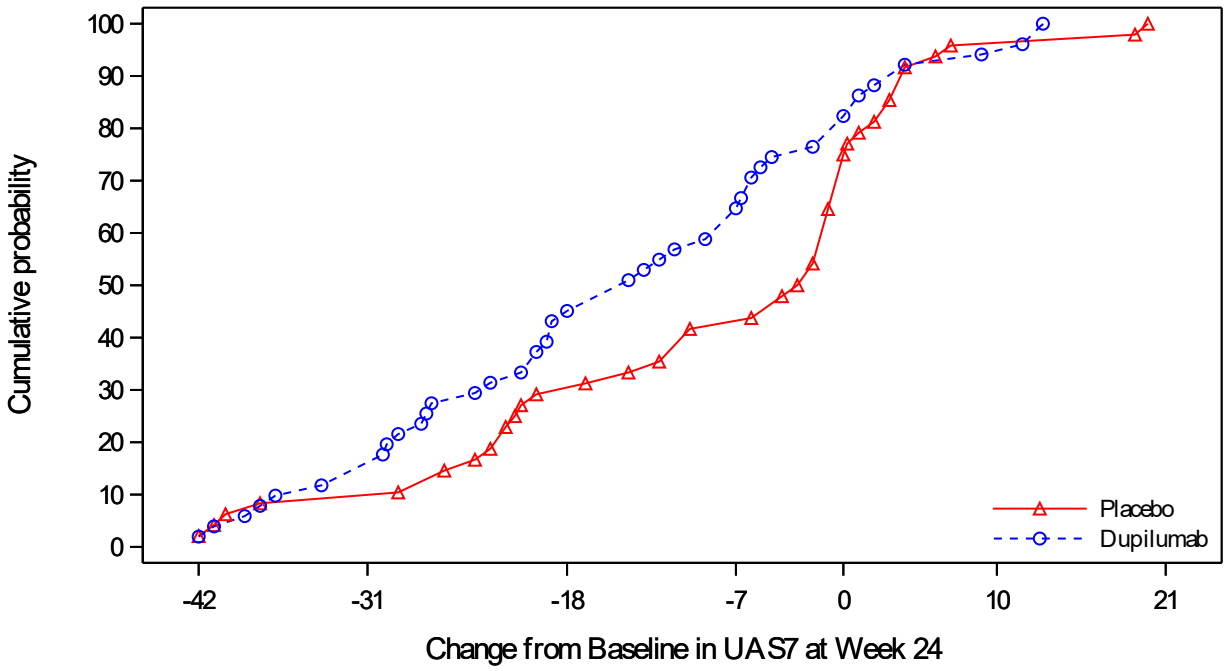


Post-hoc cumulative probability function analysis

Post-hoc categorical change analyses were conducted for UAS7 score based on a variety of responder definitions derived empirically from the study datasets. Using an anchor-based approach (PGIS as anchor), a series of clinically meaningful tresholds (CMTs) have been defined in the specific context of use in EFC16461 Study B and Study A. The estimated within-patient CMTs were as follows for UAS7: 14.00 to 18.00 point improvement for Study B and 16.87 to 21.75 point improvement for Study A. The estimated between-group CMTs for UAS7 were 6.75 to 9.4 for Study B and 12.31 to 16.17 for Study A.

The cumulative probability function of change curve displays a continuous view of the absolute change in UAS7 scores from baseline to Week 24. In EFC16461 Study B, across all possible within-patient change thresholds defined for UAS7 including previously published MID and Study B derived CMTs as well, a clear separation is observed between the dupilumab group versus the placebo group. Approximately 15%-20% greater responders are noted in the dupilumab group across the range of CMTs defined in the specific context of use in Study B (see Figure 28 below).

Figure 28. Cumulative probability function of change from baseline in UAS7 at Week 24 – ITT population – EFC16461 Study B



#Participants(%) with change less than or equal to

Placebo	1(2.1%)	4(8.3%)	14(29.2%)	20(41.7%)	36(75.0%)	46(95.8%)	48(100%)
Dupilumab	1(2.0%)	6(11.8%)	23(45.1%)	33(64.7%)	42(82.4%)	48(94.1%)	51(100%)

Post-hoc between-group difference

The UAS7 treatment difference of -5.83 (95% CI: -11.37, -0.30) were below the absolute CMTs (6.75 to 9.48 between-group difference).

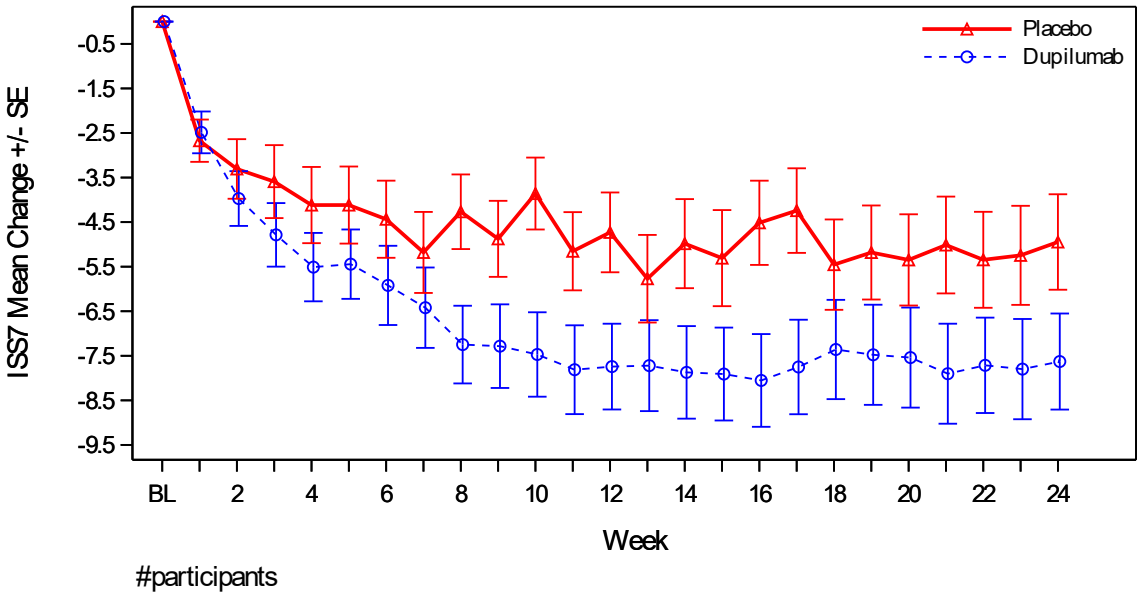
Secondary efficacy endpoints

Change from baseline in ISS7 at Week 24

Baseline mean ISS7 scores were 15.86 and 16.19 in the dupilumab and the placebo group, respectively. The LS mean change from baseline in ISS7 at Week 24 was -7.68 in the dupilumab group

versus -4.81 in the placebo group; the difference was -2.87 (95% CI: -5.68, -0.07, p=0.0449) (not meeting the SAP specified threshold of p<0.0430). Dupilumab treatment led to a reduction over time in mean ISS7 through the 24-week treatment period.

Figure 29. Plot of mean change from baseline in ISS7 over time during the 24-week treatment period - ITT population – EFC16461 Study B



#participants

Placebo	54	54	54	53	50	53	53	51	50	51	49	47	48
Dupilumab	54	54	54	53	52	53	52	50	51	49	50	51	51

PGM=PRODOPS/SAR231893/EFC16461/CSR_B4/REPORT/PGM/eff_sum_vis_all24_i_g.sas
OUT=REPORT/OUTPUT/eff_sum_iss7_all24_i_g_i.rtf (10OCT2022 14:26)

Proportion of ISS7 minimal important difference (MID) (≥5 points) responders at Week 24

Approximately 20% more participants treated with dupilumab versus placebo reached an ISS7 MID response at Week 24 (32/54 (59.3%) versus 21/54 (38.9%)), with an OR versus placebo of 1.987 (95% CI: 0.835, 4.729; nominal p=0.1203).

Post-hoc cumulative probability function analysis

Using an anchor-based approach (PGIS as the anchor), a series of CMTs have been defined in the specific context of use in Study B. The estimated within-patient CMTs for ISS7 for Study B were 7.00 to 10.50 point improvement. The estimated between-group CMTs for ISS7 was 3.82 to 5.10. Across all possible within-patient change thresholds defined for ISS7 including previously published MID and Study B derived CMTs as well, a clear separation is observed between the dupilumab group versus the placebo group. Approximately 20% greater respondents are noted in the dupilumab group across the range of CMTs defined in the specific context of use in Study B.

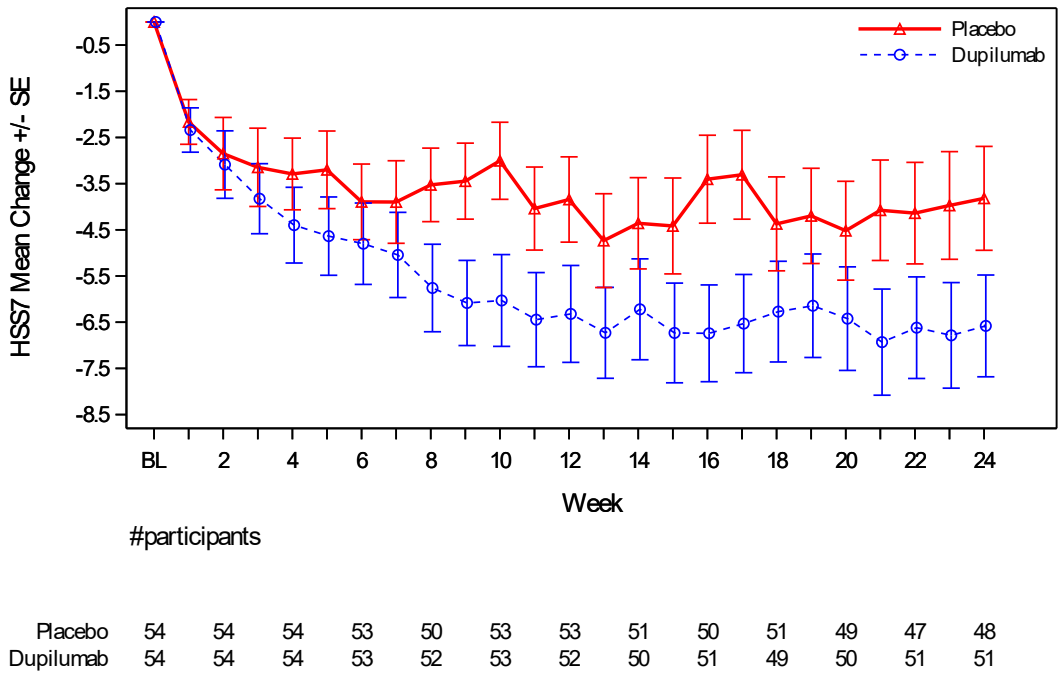
Post-hoc between-group difference

The ISS7 treatment differences of -2.87 (95% CI: -5.68, -0.07) were below the absolute CMTs 3.82 to 5.10 between-group difference.

Change from baseline in HSS7 at Week 24

Baseline mean HSS7 was 15.13 and 15.74 in the dupilumab and placebo groups, respectively. The LS mean change from baseline in HSS7 at Week 24 was -6.64 in the dupilumab group versus -3.63 in the placebo group. The LS mean difference versus placebo was -3.01, (95% CI: -5.88, -0.14, nominal p=0.0397). Dupilumab treatment led to a reduction over time in mean HSS7 through the 24-week treatment period.

Figure 30. Plot of mean change from baseline in HSS7 over time during the 24-week treatment period - ITT population – EFC16461 Study B



Placebo	54	54	54	53	50	53	53	51	50	51	49	47	48
Dupilumab	54	54	54	53	52	53	52	50	51	49	50	51	51

PGM=PRODOPS/SAR231893/EFC16461/CSR_B4/REPORT/PGM/eff_sum_vis_all24_i_g.sas
OUT=REPORT/OUTPUT/eff_sum_hss7_all24_i_g_i.rtf (10OCT2022 14:26)

Post-hoc cumulative probability function analysis

Using an anchor-based approach (PGIS as the anchor), a series of CMTs have been defined in the specific context of use in Study B, the estimated within-patient CMTs for Study B were as follows for HSS7: 6.38 to 8.00 point improvement. The estimated between-group CMT was 4.37. Across all possible within-patient change thresholds defined for HSS7 including previously published MID and Study B derived CMTs as well, a clear separation is observed between the dupilumab group versus the placebo group. Approximately 15%-20% greater respondents are noted in the dupilumab group across the range of CMTs defined in the specific context of use in Study B.

Post-hoc between-group difference

The HSS7 treatment difference of -3.01 (95% CI: -5.88, -0.14) were below to absolute CMTs 4.37 between-group difference.

Change from baseline in UCT at Week 24

At baseline, the urticaria symptoms for participants in both groups were not controlled (UCT <12) with a median baseline UCT score of 4.00 for both the dupilumab and placebo groups. At Week 24, the median UCT score was 11.00 in the dupilumab group versus 7.50 in the placebo group. The LS mean (SE) increase from baseline in UCT at Week 24 was 5.33 (0.77) in the dupilumab group versus 3.38

(0.74) in the placebo group. The LS mean difference versus placebo (95% CI) was 1.94 (-0.03, 3.92), with a nominal p-value of 0.0534.

At Week 24, 44.4% of participants in the dupilumab group improved to the well-controlled status (UCT ≥12) for their urticaria disease versus 20.4% in the placebo group, with an OR versus placebo of 2.381 (95% CI: 0.872, 6.501); nominal p = 0.0931.

Angioedema activity score over 7 days (AAS7) at Week 24

At baseline, only 20 (37.0%) participants in the dupilumab group and 33 (61.1%) of participants in the placebo group had active angioedema (AAS7 score >0), with a mean AAS7 score of 38.00 and 42.94, respectively. At Week 24, the LS mean change (decrease) from baseline in AAS7 was -16.29 in the dupilumab group and -16.54 in the placebo group, showing no difference between the two groups.

Chronic urticaria quality of life (CU-Q2oL)

Baseline mean CU-Q2oL was 42.74 and 44.36 in the dupilumab and placebo groups, respectively. A numerical trend in CU-Q2oL was observed in participants treated with dupilumab (LS mean change from baseline of -20.67) as compared to the placebo group (LS mean change from baseline of -16.52) at Week 24 (LS mean difference versus placebo of -4.15 [95% CI: -11.79; 3.49], nominal p=0.2873).

Patient Global Impression of Change (PGIC) and Patient Global Impression of Severity (PGIS)

The LS mean difference versus placebo in PGIC was -0.38 (95% CI: -1.01; 0.26; nominal p=0.2465. The Baseline mean PGIS was 3.37 and 3.39 in the dupilumab and placebo groups, respectively. The LS mean difference versus placebo in PGIS was -0.38 (95% CI: -0.78; 0.02, nominal p=0.0616).

Dermatology Life Quality Index (DLQI)

Baseline mean DLQI was 13.14 and 13.84 in the dupilumab and placebo groups, respectively. A numerical trend in dermatology-specific health-related quality-of-life as measured by DLQI was observed for participants in the dupilumab group (LS mean change from baseline of -7.08) as compared to the placebo group (LS mean change from baseline of -5.14) at Week 24 (LS mean difference versus placebo of -1.94 [95% CI: -4.51; 0.64], nominal p=0.1406).

Additional efficacy analysis

H1-antihistamine use as rescue treatment

The initial background antihistamine dose had to remain stable throughout the study and participants had to continue their maintenance dose once rescue treatment was no longer required.

At baseline, all participants were receiving H1-antihistamines for CSU, with 36.4% on standard dose and 63.6% on 2- to 4-fold of standard dose. Only 1 participant in the dupilumab group required increased H1-antihistamine dose for rescue as per the Investigator during the treatment period. Based on the e-diary data as an alternative to capture potential H1-antihistamine dose increase, similar number of participants on dupilumab reported an H1-antihistamine dose increase for more than or equal to 3 consecutive days compared to participants on placebo (dupilumab: 13 (24.1%); placebo: 12 (22.2%).

Corticosteroid use

Overall use of OCS was low as rescue treatment for symptoms of CSU. There were 2 (3.7%) participants requiring OCS rescue during the treatment period for the dupilumab group compared to 5 (9.3%) participants in the placebo group.

Treatment effect after study intervention discontinuation

Change from baseline in ISS7 and UAS7 post-treatment

In Study B, a total of 40 participants in the dupilumab group and 44 participants in the placebo group reported post-intervention data at Week 36 for UAS7, ISS7, and HSS7. Post treatment, the residual treatment effects diminished gradually, but did not return to baseline by the end of the 12-week follow-up period in both intervention groups. The mean ISS7 and UAS7 scores in the dupilumab group remained numerically lower compared with the placebo group during the 12-week follow-up period.

Ancillary analyses

Interim Analysis

The interim analysis population for the efficacy endpoints was the ITT24 population, defined as all participants who were randomized at least 24 weeks before the IA cut-off date and would have completed the Week 24 visit by the IA cut-off date.

The interim analysis (cut-off date: 17 Dec 2021) met the protocol specified statistical criteria for futility:

- UAS7: The LS mean difference versus placebo for change from baseline at Week 24 was -3.15 (95% CI: -9.79, 3.49), p=0.3529; which was not statistically significant and met futility criteria of p >0.1.
- ISS7: The LS mean difference versus placebo for change from baseline at Week 24 was -1.96 (95% CI: -5.33, 1.42), p=0.2555; which was not statistically significant.

The Sponsor sent a notification to investigators and sites dated 18 February 2022 with instructions that the investigators were to contact and inform participants who were still receiving study treatment and organize an early End of Treatment (EOT) visit. A public IA futility announcement (press release dated 18 February 2022) was issued the same day stating that patients will stop due to futility based on a pre-specified interim analysis.

Three participants (out of the 25 participants not included in the IA) discontinued due to IA futility announcement. A final data analysis including all the randomized participants' data based on the final database lock was conducted.

Table 26. Interim Analysis - Change from baseline in UAS7 at Week 24 - ITT24 population – EFC16461 Study B

UAS7	Placebo (N=40)	Dupilumab (N=43)
Baseline		
Number	40	43
Mean (SD)	32.75 (7.51)	30.70 (8.03)
Median	32.50	31.00
Q1 ; Q3	27.00 ; 40.50	24.00 ; 38.00
Min ; Max	16.0 ; 42.0	16.0 ; 42.0
Week 24		
Number	36	39
Mean (SD)	22.41 (15.08)	17.61 (14.05)
Median	26.60	14.00
Q1 ; Q3	7.00 ; 36.00	7.00 ; 29.00
Min ; Max	0.0 ; 42.0	0.0 ; 42.0
Change from baseline		
Number (observed/imputed)	36 (28/8)	39 (31/8)
Mean (SD)	-10.76 (13.86)	-12.95 (15.07)
Median	-5.00	-12.00

UAS7	Placebo (N=40)	Dupilumab (N=43)
Q1 ; Q3	-21.70 ; 0.00	-23.00 ; 0.00
Min ; Max	-42.0 ; 6.0	-42.0 ; 13.0
LS Mean (SE) [a]	-10.12 (2.51)	-13.26 (2.44)
LS Mean Diff vs. placebo (95% CI) [a]		-3.15 (-9.79, 3.49)
P-value vs. placebo [a]		0.3529

WOCF: Worst observation carried forward; MI: Multiple imputation

a Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, presence of angioedema at baseline, and regions as covariates.

Note: Data collected after study intervention discontinuation were included. Data post select prohibited/rescue medications were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF; other missing data were imputed by MI. Descriptive statistics at Week 24 include participants after WOCF at Week 24, and participants whose values were imputed by MI at Week 24 were excluded from the descriptive analysis.

PGM=PRODOPS/SAR231893/EFC16461/CSR_B2/REPORT/PGM/eff_ancova_i_t.sas

OUT=REPORT/OUTPUT/eff_ancova_uas7_wk24_i_t_i.rtf (13SEP2022 6:07)

The key dates for the IA included the following:

- Per protocol, only those patients who completed or would have completed their Week 24 visit on or before the IA cut-off (17 Dec 2021) were included in the interim analysis (N=83).
- the IA DBL occurred on 19 January 2022,
- the IA Review Committee (IARC) Outcome was provided on 25 January 2022,
- an analysis by a limited Sponsor unblinded team occurred on 27 January, and press release of the IA futility announcement was issued on 18 February 2022.

Change from baseline in UAS7 at Week 24 for participants in the period between the IA data cut-off and 18-Feb-2022

Among the 25 participants not included in the IA, 10 participants had completed or discontinued treatment before the IA futility announcement (1 discontinued and 9 completed EOT visits per protocol between the IA cut-off date and the IA futility announcement). Of the other 15 who were still on treatment at 12 different study sites, 3 discontinued study intervention early as a result of the IA futility announcement, and for 12 participants, the investigators and patients continued their home-administered IMP until the EOT visit. All 12 EOT visits were completed by 24 March 2022, which was approximately one month after the IA futility announcement on 18 February 2022.

Changes from baseline in UAS7 for Week 24 visits for the remaining participants obtained after the interim analysis are shown below.

Table 27. Change from baseline in UAS7 at Week 24 – EFC16461 Study B – Non-ITT24 population who completed Week 24 visit between the IA data cut-off and 18 Feb 2022

UAS7	Placebo (N=6)	Dupilumab (N=4)
Baseline		
Number	6	4
Mean (SD)	33.33 (10.19)	36.50 (3.70)
Median	37.50	35.00
Q1 ; Q3	21.00 ; 42.00	34.50 ; 38.50
Min ; Max	20.0 ; 42.0	34.0 ; 42.0
Week 24		
Number	6	4
Mean (SD)	25.47 (17.14)	19.31 (10.57)
Median	27.50	15.00
Q1 ; Q3	14.00 ; 40.83	13.13 ; 25.50
Min ; Max	1.0 ; 42.0	12.3 ; 35.0
Change from baseline		
Number (observed/imputed)	6 (4/2)	4 (4/0)
Mean (SD)	-7.86 (21.08)	-17.19 (12.44)
Median	-3.50	-19.50
Q1 ; Q3	-22.00 ; 3.00	-24.88 ; -9.50
Min ; Max	-41.0 ; 19.8	-29.8 ; 0.0
LS Mean (SE) [a]	NE	NE
LS Mean Diff vs. placebo (95% CI) [a]		NE
P-value vs. placebo [a]		NE

WOCF: Worst observation carried forward; MI: Multiple imputation; NE: Not Evaluable
[a] Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, presence of angioedema at baseline, and regions as covariates.
Note: Data collected after study intervention discontinuation were included. Data post select prohibited/rescue medications were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF; other missing data were imputed by MI. Descriptive statistics at each week include participants after WOCF at the week, and participants whose values were imputed by MI at the week were excluded from the descriptive analysis.
PGM=PRODOPS/SAR231893/OVERALL/CSU_EMA_2024/REPORT/PGM/eff_ancova_sb_ni_i_t.sas
OUT=REPORT/OUTPUT/eff_ancova_uas7_wk24_sb_nino_i_t_i.rtf (21JUN2024 5:36)

Table 28. Change from baseline in UAS7 at Week 24 – EFC16461 Study B – Non-ITT24 population who completed Week 24 after the 18 Feb 2022

UAS7	Placebo (N=8)	Dupilumab (N=7)
Baseline		
Number	8	7
Mean (SD)	26.75 (8.41)	29.62 (8.27)
Median	25.00	31.00
Q1 ; Q3	19.50 ; 32.00	20.00 ; 37.00
Min ; Max	19.0 ; 42.0	16.3 ; 37.0
Week 24		
Number	6	7
Mean (SD)	31.33 (11.71)	11.50 (9.43)
Median	33.00	7.00
Q1 ; Q3	26.00 ; 42.00	3.50 ; 20.00
Min ; Max	12.0 ; 42.0	3.0 ; 28.0
Change from baseline		
Number (observed/imputed)	6 (4/2)	7 (7/0)
Mean (SD)	2.17 (9.87)	-18.12 (16.64)
Median	-0.50	-27.50
Q1 ; Q3	-2.00 ; 7.00	-30.00 ; -7.00
Min ; Max	-10.0 ; 19.0	-34.0 ; 11.7
LS Mean (SE) [a]	-1.99 (5.18)	-18.51 (4.94)
LS Mean Diff vs. placebo (95% CI) [a]		-16.52 (-29.50, -3.54)
P-value vs. placebo [a]		0.0126

WOCF: Worst observation carried forward; MI: Multiple imputation
[a] Each of the imputed complete data were analyzed by fitting an ANCOVA model with the corresponding baseline value, intervention group, presence of angioedema at baseline, and regions as covariates.
Note: Data collected after study intervention discontinuation were included. Data post select prohibited/rescue medications were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF; other missing data were imputed by MI. Descriptive statistics at each week include participants after WOCF at the week, and participants whose values were imputed by MI at the week were excluded from the descriptive analysis.
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OUT=REPORT/OUTPUT/eff_ancova_uas7_wk24_sb_nion_i_t_i.rtf (21JUN2024 5:36)

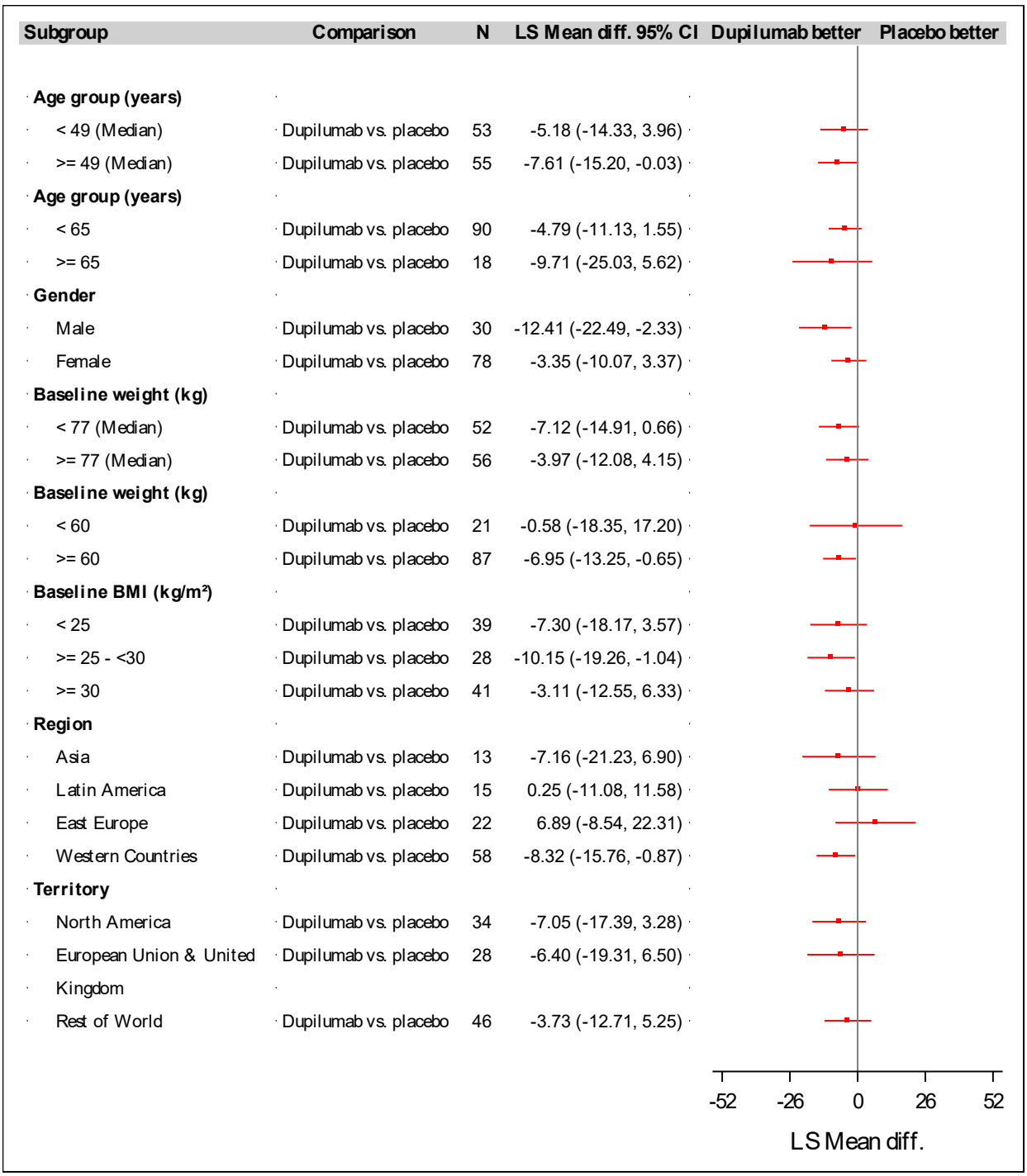
In the period between the IA data cut-off and 18-Feb-2022, the mean change from baseline was -7.86 in the placebo group vs -17.19 in the dupilumab group. In the period after 18-Feb-2022, the mean change from baseline was 2.17 in placebo and -18.12 in the dupilumab group leading to large treatment effect favouring dupilumab.

Subgroup analysis

Change from baseline in UAS7 at Week 24 by subgroups

Most subgroups showed a numerically greater treatment effect of dupilumab as compared with placebo in UAS7 reduction at Week 24, except for 4 subgroups (Latin America [N=15], East Europe [N=22], Baseline H1-antihistamines standard dose [N=39], and Baseline median IgE <77 IU/mL [N=52]) which showed either a numerically larger change from baseline in the placebo group compared to the dupilumab group or wide confidence intervals.

Figure 31. Plot of treatment effect on change from baseline in UAS7 at Week 24 by subgroups - ITT population – EFC16461 Study B



PGM=PRODOPS/SAR231893/EFC16461/CSR_B4/REPORT/PGM/eff_ancova_sub_i_g.sas
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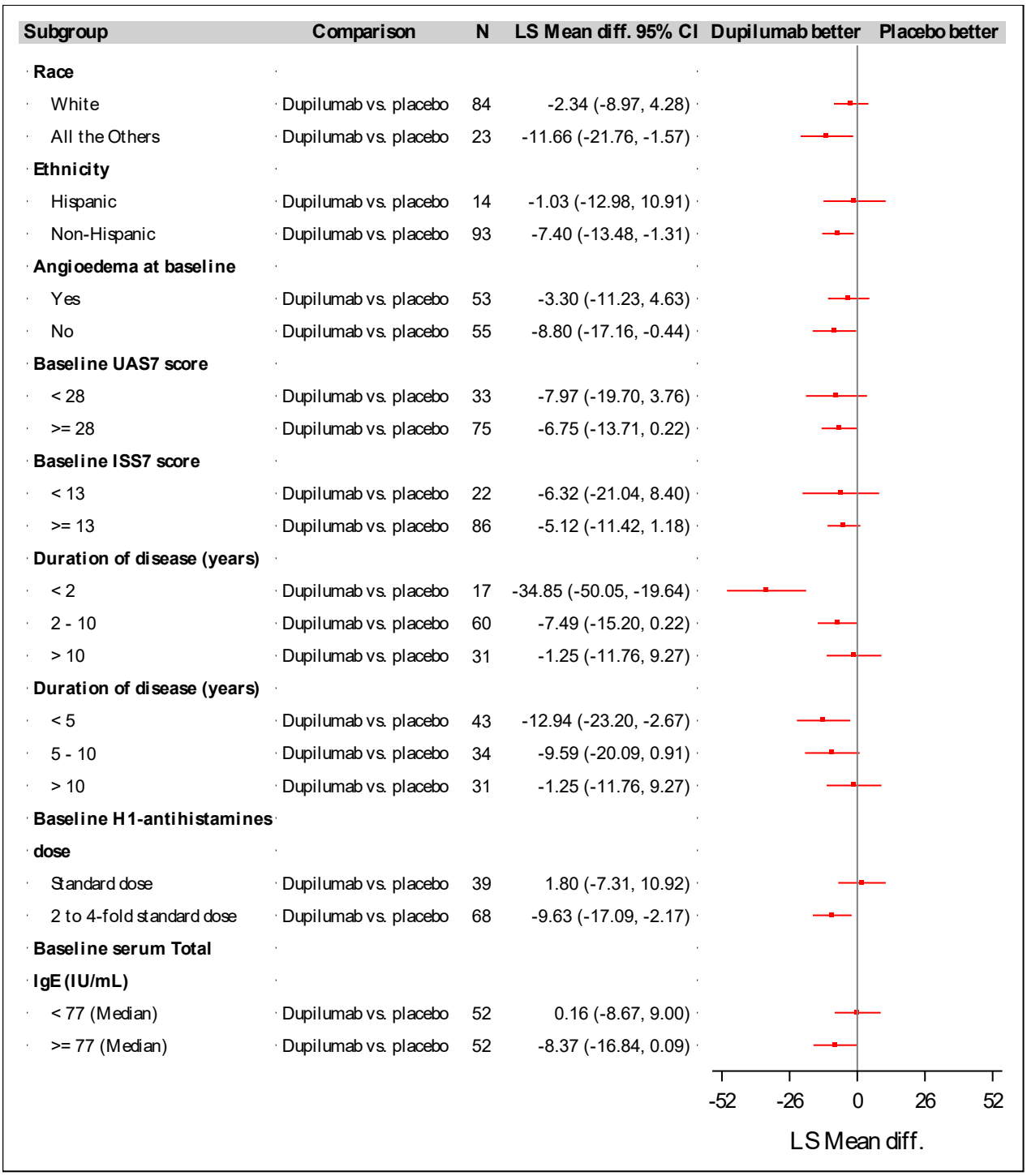


Change from baseline in ISS7 at Week 24 by subgroups

Most subgroups showed a numerically greater treatment effect of dupilumab as compared with placebo in ISS7 reduction at Week 24, except for 5 subgroups (Latin America [N=15], East Europe [N=22], Hispanic ethnicity [N=14], Baseline H1-antihistamine standard dose [N=39], and Baseline median IgE <77 IU/mL [N=52]) which showed either a numerically larger change from baseline in the placebo group compared to the dupilumab group or wide confidence intervals.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 29. Summary of Efficacy for trial EFC16461 Study B

Title: A randomized, double-blind, placebo-controlled, multi-centre, parallel-group studies of dupilumab in patients with chronic spontaneous urticaria (CSU) show remain symptomatic despite the use of H1 antihistamine treatment in patients who are intolerant or incomplete responders to omalizumab **(LIBERTY CSU-CUPID Study B)**			
Study identifier	EFC 16461 B EudraCT: 2019-003775-19		
Design	EFC16461 Study B was a 24-week, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of dupilumab in adult and adolescent participants with CSU who remained symptomatic despite the use of H1-antihistamine and who were intolerant or incomplete responders to omalizumab. Participants were considered as intolerant or incomplete responders to omalizumab if they were treated for CSU with at least 300 mg (q4w) of omalizumab for at least 3 months (minimum of 3 injections) and had an inadequate response or were intolerant, resulting in treatment discontinuation, as confirmed by Investigator assessment.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks not applicable not applicable	
Hypothesis	Superiority		
Treatments groups	Dupilumab	Dupilumab 300 mg Q2W, 24-week treatment period, 54 on dupilumab (54 on 300 mg q2w, 0 on 200 mg q2w)	
	Placebo	Matching placebo Q2W, 24-week treatment period, 54 randomized participants	
Endpoints and definitions	Primary endpoint	UAS7 at Week 24	Change from baseline in UAS7 at Week 24
	Secondary endpoint	ISS7 at Week 24	Change from baseline in ISS7 at Week 24
	Secondary endpoint	HSS7 at Week 24	Change from baseline in HSS7 at Week 24
	Secondary endpoint	MID at Week 24	Proportion of participants with MID (ISS7 ≥ 5) response at Week 24
	Secondary endpoint	UAS7 ≤ 6 at Week 24	Proportion of participants with UAS7 ≤ 6 at Week 24
	Secondary endpoint	UAS7 = 0 at Week 24	Proportion of participants with UAS7 = 0 at Week 24
	Secondary endpoint	UCT at Week 24	Change from baseline in UCT at Week 24
Database lock	18 July 2022		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat population		
Descriptive statistics and estimate variability	Treatment group	Placebo	Dupilumab
	Number of subjects	54	54
	Primary endpoint: Change from baseline in UAS7 at Week 24	-8.54 (2.14)	-14.37 (2.16)
	95% CI	-12.74 to -4.34	-18.60 to -10.15

Effect estimate per comparison	Primary endpoint: Change from baseline in UAS7 at Week 24	Comparison groups	Dupilumab vs Placebo
		Least square means difference (95% CI)	-5.83 (-11.37, -0.30)
		P-value	0.0390
Analysis description	**Secondary Analysis**		
Analysis population and time point description	Intent to treat population		
Descriptive statistics and estimate variability	Treatment group	Placebo	Dupilumab
	Number of subjects	54	54
	Change from baseline in ISS7 at Week 24	-4.81 (1.08)	-7.68 (1.10)
	95% CI	-6.93 to -2.68	-9.83 to -5.53
	Change from baseline in HSS7 at Week 24	-3.63 (1.11)	-6.64 (1.11)
	95% CI	-5.80 to -1.45	-8.82 to -4.45
	Proportion of participants with MID (ISS7 reduction ≥ 5) response at Week 24	21 (38.9)	32 (59.3)
	95% CI	25.9 to 53.1	45.0 to 72.4
	Proportion of participants with UAS7 ≤ 6 at Week 24	10 (18.5)	13 (24.1)
	95% CI	9.3 to 31.4	13.5 to 37.6
	Proportion of participants with UAS7 = 0 at Week 24	5 (9.3)	7 (13.0)
	95% CI	3.1 to 20.3	5.4 to 24.9
	Change from baseline in UCT at Week 24	3.38 (0.74)	5.33 (0.77)
	95% CI	1.94 to 4.82	3.82 to 6.83
Effect estimate per comparison		Comparison groups	Dupilumab vs Placebo
	Change from baseline in ISS7 at Week 24	Least square means difference (95% CI)	-2.87 (-5.68, -0.07)
		P-value	0.0449
	Change from baseline in HSS7 at Week 24	Least square means difference (95% CI)	-3.01 (-5.88, -0.14)
		p-value	0.0397
	Proportion of participants with MID (ISS7 reduction ≥ 5)	Odds ratio (95% CI)	1.987 (0.835, 4.729)

	response at Week 24		
		p-value	0.1203
	Proportion of participants with UAS7 ≤ 6 at Week 24	Odds ratio (95% CI)	1.899 (0.577, 6.247)
		p-value	0.3107
	Proportion of participants with UAS7 = 0 at Week 24	Odds ratio (95% CI)	1.180 (0.268, 5.201)
		p-value	0.8373
	Change from baseline in UCT at Week 24	Least square means difference (95% CI)	1.94 (-0.03, 3.92)
		p-value	0.0534

Clinical studies in special populations

Efficacy data for adolescents (aged ≥12 years and <18 years)

Overall, 2 adolescents (≥12 to <18 years old) (1 in each intervention group) were enrolled in Study B and completed the treatment period of the study.

The 2 adolescents had nearly identical baseline values in ISS7, HSS7, and UAS7. During the treatment period, numerical improvements (decreases) in ISS7, HSS7, and UAS7 were observed in both participants. For the adolescent in the dupilumab group, a greater initial improvement was seen in ISS7, HSS7, and UAS7 by Week 12 (compared with the adolescent in the placebo group).

Table 30. Listing of e-diary data (ISS7, HSS7, UAS7) and questionnaire data (UCT) in adolescents - ITT population – EFC16461 Study B

Participant	Intervention group	Age (yrs)/ Sex[a]/ Weight	Timepoint	ISS7	HSS7	UAS7	AAS7	UCT
Adolescents								
Adolescent 1	Placebo	/	Baseline	15	21	36	0	4
			Week 12	13	13	26	0	10
			Week 24	7	7	14	0	15
Adolescent 2	Dupilumab 300 mg q2w	/	Baseline	14	21	35	0	6
			Week 12	1	1	2	4	12
			Week 24	11	5	16	0	12

ISS7: itch-severity score over 7 days (0-21); UAS7: urticaria activity score over 7 days (0-42); HSS7: hives-severity score over 7 days (0-21); AAS7: angioedema activity score over 7 days (0-105); UCT: urticaria control test (0-16).

a M=Male, F=Female.

Extracted from: PGM=PRODOPS/SAR231893/EFC16461/CSR_B4/REPORT/PGM/eff_diary_ado_i_l.sas OUT=REPORT/OUTPUT/eff_diary_ado_i_l_i.rtf (08AUG2022 4:21)
and PGM=PRODOPS/SAR231893/EFC16461/CSR_B4/REPORT/PGM/eff_qs_ado_i_l.sas OUT=REPORT/OUTPUT/eff_qs_ado_i_l_i.rtf (08AUG2022 4:21)

2.4.2.3. EFC16461 Study A (supportive)

EFC16461 Study A was a 24-week, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of dupilumab in participants with CSU who remained symptomatic despite the use of H1-antihistamine and who were naïve to omalizumab.

Study A was conducted together with Study B (see 5.4.2.1) under one master protocol (EFC16461) and included overall the same design elements as Study B with a different study population recruited. Differences in study design as compared to Study B are described in the following.

Methods

See Study B

Study participants

The same inclusion and exclusion criteria as for Study B were used with the following exceptions:

- Study A enrolled adult and pediatric patients aged ≥6 to <18 years
- Study A enrolled participants who were omalizumab naïve.

Treatments

Same treatment and background or rescue medication as within Study B.

Objectives / Outcomes and Endpoints

Same objectives and endpoints as for Study B.

Sample size

Same sample size calculation as in Part B. The anticipated sample size was 104.

Randomisation

All participants were centrally assigned to randomized study intervention using an interactive response technology (IRT). Sanofi generated the randomized intervention kit number list centrally and IMPs (dupilumab 300 mg, dupilumab 200 mg, or their matching placebo) are packaged in accordance with this list. The IRT generated the participant randomization list and allocated the intervention number and the corresponding intervention kits to the participants according to it.

Participants were randomized in a 1:1 ratio to intervention or control group, respectively. The randomization was stratified first by age (adults versus adolescents versus children; up to approximately 5% of total sample size for children and approximately 5% of total sample size for adolescents). In adults, randomization was stratified further by country. In adolescents/children ≥6 to <12 years of age, randomization will not be stratified further. In Study A, overall 52% of participants received H1-AH at recommended doses as background therapy, and 45% of participants presented with angioedema at baseline. A randomized participant was defined as a participant who has been allocated to a randomized

intervention regardless whether the treatment was administered or not (ie, participant registered by the IRT).

Blinding (masking)

Same blinding procedures as in Study B.

Statistical methods

Analysis Populations

Same as in Study B.

Primary and secondary Estimands

The primary efficacy endpoints were analyzed using an analysis of covariance (ANCOVA) model with the baseline value of the primary endpoint, intervention group, presence of angioedema at baseline, and region as covariates, with intercurrent events and missing data being handled by a hybrid method of the worst-observation carried forward (WOCF) and multiple imputation.

Strategies for handling intercurrent events and missing values were the same as in study B.

Supplementary Analysis for Primary Endpoint

The same sensitivity analyses are conducted as in study B (described above) (except for the Tipping point analysis on WOCF):

1. Pattern mixture model with copy increment from placebo after WOCF
2. Pattern mixture model with copy increment from placebo without WOCF
3. Tipping point analysis for missing data

Additionally, an as-observed analysis was conducted (as in study B and described above).

Multiplicity

A multiplicity procedure is proposed to control the overall type-I error rate for testing the primary and selected secondary endpoints. The overall alpha is 0.05. The comparisons with placebo will be tested based on the hierarchical order below at 2-sided $\alpha = 0.05$:

1. Change from baseline in UAS7 at Week 24

2. Change from baseline in ISS7 at Week 24

3. Proportion of patients with UAS7 ≤6 at Week 24

4. Proportion of patients with UAS7 = 0 at Week 24

5. Change from baseline in HSS7 at Week 24

6. Change from baseline in ISS7 at Week 12

7. Change from baseline in UAS7 at Week 12

8. Proportion of patients with UAS7 ≤6 at Week 12

9. Proportion of patients with MID (ISS7 ≥5) response at Week 24

10. Proportion of patients with MID (ISS7 ≥5) response at Week 12

11. Change from baseline in HSS7 at Week 12

12. Proportion of patients with UAS7 = 0 at Week 12

13. Change from baseline in UCT at Week 24

14. Change from baseline in UCT at Week 12

Study A is considered positive when the primary endpoint (change from baseline in UAS7 at Week 24) achieves statistical significance.

Subgroup Analyses

Same subgroup analyses as in study B.

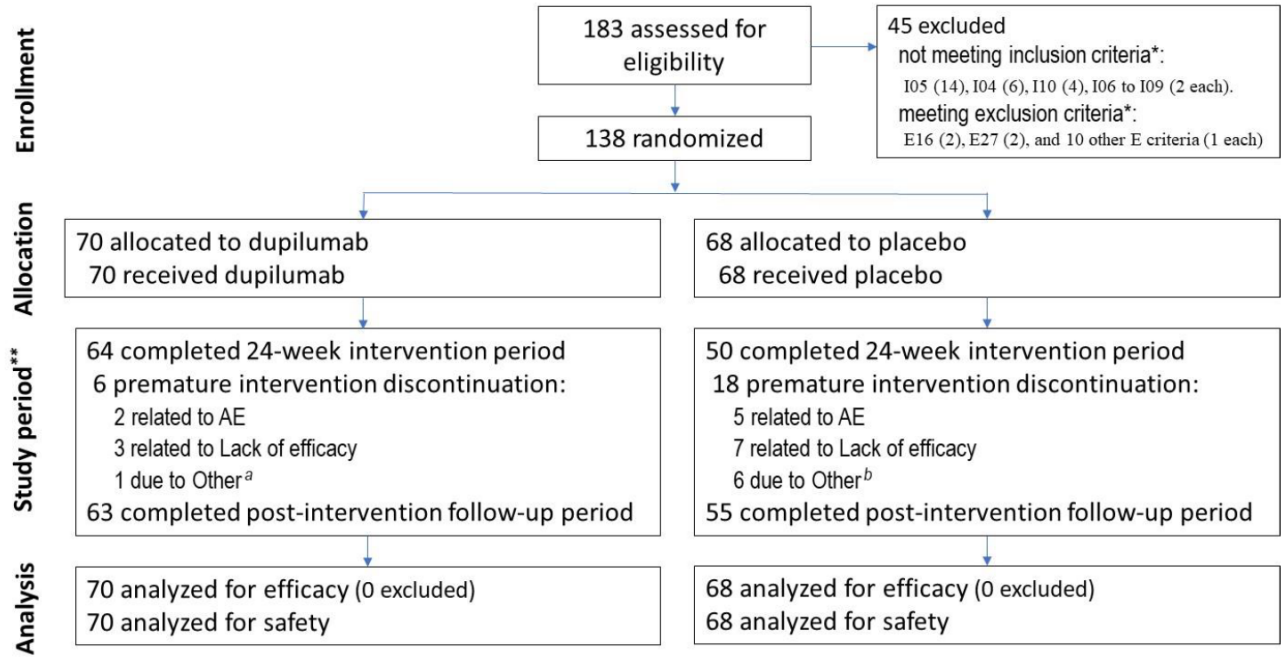
2.4.2.4. Results

Participant flow

A total of 138 participants (including 4 adolescents aged ≥12 and <18 years and 2 children aged ≥6 and <12 years) were randomized to study intervention: 70 in the dupilumab group and 68 in the placebo group. Out of 183 participants screened, 45 were screen failures. The most frequent reason for screen failure was not meeting inclusion criterion I 05 (UAS7 ≥16 and ISS7 ≥8 during 7 days before randomization) (7.7% of participants screened). In the randomized population, the rate of premature discontinuation of study intervention was lower in the dupilumab group compared with the placebo group (8.6% vs. 26.5%).

Of the 24 participants (6 in the dupilumab group and 18 in the placebo group) who prematurely discontinued study intervention, 17 participants (6 in the dupilumab group and 11 in the placebo group) also discontinued the study prematurely (did not complete the post-treatment follow-up period), including 2 lost to follow-up (1 in each group). The other 7 participants (all in the placebo group) completed the follow-up period and the study. Of the 114 participants who completed the 24-week treatment period, 3 participants did not complete the follow-up period (1 in placebo group due to AE and 2 [1 in each group] per Withdrawal by subject).

Figure 32. Patient Disposition EFC16461 Study A



Source: Table 6 and Appendix 16.2.1 Participant disposition, Tables 16.2.1.1, 16.2.1.3, 16.2.1.5, 16.2.1.6.

* Refer to Section 3.3.1 for definitions of Inclusion and Exclusion criteria.

** Study period = study intervention period + post-intervention follow-up period.

a Discontinued IMP due to "patient did not return paper diaries or IP boxes to the site"

b 2 participants discontinued IMP due to "usage of prohibited therapy levilimab" and "lost to follow-up", respectively, and 4 participants discontinued IMP per Withdrawal by subject for other reasons (other than adverse event or lack of efficacy).

Recruitment

EFC16461 Study A

First participant enrolled:	06 February 2020
Last participant (end of treatment visit):	26 August 2021
The primary analysis data cut-off:	05 October 2021

Conduct of the study

Protocol amendments (related to Study A)

The original master protocol dated 24 October 2019 was modified per 3 global amendments (amendment 02 dated 30 April 2020, amendment 04 dated 29 April 2021, amendment 05 dated 17 March 2022) and 2 local amendments (amendment 01 for Japan dated 10 February 2020, amendment 03 for France dated 09 October 2020).

Amendment 02 included a switch of the primary and the key secondary endpoints to establish the weekly urticaria activity score (UAS7) as the primary endpoint for European Union (EU) and EU reference countries based on recommendations from European Medicines Agency (EMA). Amendment 04 and Amendment 05 were not applicable to Study A.

COVID-19 pandemic

EFC16461 Study A was conducted during the global COVID-19 pandemic which began in March 2020. The study began in February 2020 and continued without stoppage during the global COVID-19 pandemic. The overall impact of the pandemic however was minimal on the conduct of EFC16461 Study B, in terms of the ability to retain participants on study treatment, to complete study visits, to conduct study monitoring, and to collect and verify the efficacy and safety data. The integrity of the study data and the scientific validity of the study remained intact.

Protocol deviations

Major protocol deviations were reported in 12 (17.1%) participants in the dupilumab group and 10 (14.7%) in the placebo group. The most frequently reported major protocol deviations were in the categories of "Assessments/procedures" (2 [2.9%] participants in the dupilumab group and 5 [7.4%] in the placebo group), "Concomitant medications/therapy" (4 [5.7%] and 2 [2.9%], respectively), and "Inclusion/exclusion criteria" (4 [5.7%] and 2 [2.9%]). There were no deviations assessed as critical in this study.

Breaking of the blind

There was no breaking of the blind during the study either by the Sponsor for regulatory purposes (as there were no reported suspected unexpected serious adverse reactions [SUSAR]) or by the Investigator for safety purposes.

Baseline data

Demographics

The mean (SD) age of the participants was 41.3 (15.5) years with a range of 8 to 77 years, 65.9% were females, and the majority of participants (68.8%) were White. There were 132 adults (95.7%), 4 adolescents (≥12 to <18 years) (2.9%), and 2 children (≥6 to <12 years) (1.4%) randomized in the study. The mean body weight at screening was 76.48 kg, with 26 (19.0%) participants weighing <60 kg and 111 (81.0%) participants weighing ≥60 kg. No participants weighed <30 kg at screening.

As compared to Study B participants had an overall shorter urticaria disease duration (5.7 years vs. 9.1 years). Almost all participants in EFC16461 Study B were diagnosed more than 1 year ago (98.1%) compared to only 70.3% of participants in EFC16461 Study A. Study A participants had lower utilization of high dose antihistamines (47.8% vs. 63.6%). Study A had higher median baseline total IgE (101 IU/mL vs. 77 IU/mL).

Table 31. Demographics and participant characteristics at baseline - Randomized population – EFC16461 Study A

	Placebo (N=68)	Dupilumab (N=70)	All (N=138)
Age (years)			
Number	68	70	138
Mean (SD)	41.9 (14.8)	40.7 (16.2)	41.3 (15.5)
Median	41.0	41.5	41.0
Q1 ; Q3	28.5 ; 52.5	27.0 ; 52.0	28.0 ; 52.0
Min ; Max	12 ; 77	8 ; 75	8 ; 77
Age group (years) [n (%)]			
Number	68	70	138
6-11	0	2 (2.9)	2 (1.4)
12-17	2 (2.9)	2 (2.9)	4 (2.9)

	Placebo (N=68)	Dupilumab (N=70)	All (N=138)
18-39	30 (44.1)	28 (40.0)	58 (42.0)
40-64	32 (47.1)	30 (42.9)	62 (44.9)
65-74	3 (4.4)	7 (10.0)	10 (7.2)
≥75	1 (1.5)	1 (1.4)	2 (1.4)
Region[a] [n (%)]			
Number	68	70	138
Asia	16 (23.5)	17 (24.3)	33 (23.9)
Latin America	10 (14.7)	9 (12.9)	19 (13.8)
East Europe	12 (17.6)	11 (15.7)	23 (16.7)
Western Countries	30 (44.1)	33 (47.1)	63 (45.7)
Territory[b] [n (%)]			
Number	68	70	138
North America	27 (39.7)	29 (41.4)	56 (40.6)
European Union & United Kingdom	4 (5.9)	4 (5.7)	8 (5.8)
Rest of World	37 (54.4)	37 (52.9)	74 (53.6)
Sex [n (%)]			
Number	68	70	138
Male	18 (26.5)	29 (41.4)	47 (34.1)
Female	50 (73.5)	41 (58.6)	91 (65.9)
Race [n (%)]			
Number	68	70	138
White	48 (70.6)	47 (67.1)	95 (68.8)
Black or African American	2 (2.9)	1 (1.4)	3 (2.2)
Asian	16 (23.5)	19 (27.1)	35 (25.4)
Japanese	6 (8.8)	6 (8.6)	12 (8.7)
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaska Native	0	1 (1.4)	1 (0.7)
Multiple	1 (1.5)	1 (1.4)	2 (1.4)
Not reported	1 (1.5)	1 (1.4)	2 (1.4)
Unknown	0	0	0
Ethnicity [n (%)]			
Number	68	70	138
Hispanic or Latino	12 (17.6)	13 (18.6)	25 (18.1)
Not Hispanic or Latino	56 (82.4)	57 (81.4)	113 (81.9)
Weight (kg)			
Number	67	70	137
Mean (SD)	75.79 (18.36)	77.15 (21.49)	76.48 (19.96)
Median	72.00	74.00	73.00
Q1 ; Q3	64.50 ; 87.00	60.00 ; 92.90	63.00 ; 91.00
Min ; Max	43.0 ; 119.0	32.5 ; 135.9	32.5 ; 135.9
Weight group (kg) [n (%)]			
Number	67	70	137
<60	10 (14.9)	16 (22.9)	26 (19.0)
≥60	57 (85.1)	54 (77.1)	111 (81.0)
BMI (kg/m^2)			
Number	67	70	137

	Placebo (N=68)	Dupilumab (N=70)	All (N=138)
Mean (SD)	27.90 (6.19)	27.45 (6.77)	27.67 (6.47)
Median	27.15	26.19	26.77
Q1 ; Q3	23.15 ; 30.76	22.30 ; 31.77	22.72 ; 30.82
Min ; Max	17.6 ; 44.8	17.3 ; 53.1	17.3 ; 53.1
BMI group (kg/m^2) [n (%)]			
Number	67	70	137
<30	47 (70.1)	51 (72.9)	98 (71.5)
≥30	20 (29.9)	19 (27.1)	39 (28.5)

BMI: Body mass index

a Asia: China and Japan; Latin America: Argentina; East Europe: Russia, Hungary; Western Countries: Canada, USA, France, Germany, Spain, United Kingdom;

b North America: Canada, USA; European Union & United Kingdom: France, Germany, Hungary, Spain, United Kingdom; Rest of World: China, Japan, Argentina, Russia

PGM=PRODOPS/SAR231893/EFC16461/CSR A3/REPORT/PGM/dem demo r t.sas
OUT=REPORT/OUTPUT/dem_demo_r_t_i.rtf (04MAR2022 7:52)

Baseline disease characteristics

The mean (SD) age at onset of CSU was 36.1 (16.2) years. The mean (SD) time since first diagnosis of CSU prior to study entry was 5.7 (8.5) years; 70.3% of participants had more than 1 year of disease duration prior to study participation. The mean (SD) ISS7 and UAS7 scores at baseline were 15.9 (4.0) and 31.3 (7.7), respectively, indicative of severe itch and urticaria activity at baseline for the enrolled participants. Per protocol, all participants had at least moderate urticaria activity (UAS7 score =16 to 27 at baseline) with the vast majority of participants (70.3%) with severe urticaria activity (UAS7 score of ≥28 at baseline). A total of 62 (44.9%) participants presented with angioedema at baseline (AAS7 >0). At baseline, all participants were receiving H1-antihistamines for CSU, with 52.2% on standard approved dose, 31.2% on 2- to 3-fold of standard dose, and 16.7% on 4-fold of standard dose. The mean total IgE at baseline was 540.3 IU/mL and the median total IgE at baseline was 101.0 IU/mL.

Table 32. Disease characteristics at baseline - Randomized population – EFC16461 Study A

	Placebo (N=68)	Dupilumab (N=70)	All (N=138)
Age at onset of CSU (years)			
Number	68	70	138
Mean (SD)	36.7 (16.0)	35.5 (16.6)	36.1 (16.2)
Median	36.5	37.0	37.0
Q1 ; Q3	24.0 ; 50.0	20.0 ; 46.0	24.0 ; 50.0
Min ; Max	5 ; 77	6 ; 73	5 ; 77
Time since first diagnosis of CSU (years)			
Number	68	70	138
Mean (SD)	5.7 (7.7)	5.8 (9.3)	5.7 (8.5)
Median	2.2	2.0	2.0
Q1 ; Q3	1.0 ; 7.3	0.9 ; 5.7	0.9 ; 6.0
Min ; Max	1 ; 35	1 ; 60	1 ; 60
Baseline ISS7 score			
Number	68	70	138
Mean (SD)	15.7 (4.1)	16.1 (4.0)	15.9 (4.0)
Median	15.5	16.0	16.0
Q1 ; Q3	13.0 ; 20.0	14.0 ; 20.0	13.0 ; 20.0
Min ; Max	8 ; 21	8 ; 21	8 ; 21
Baseline ISS7 score [n (%)]			
Number	68	70	138
<13	16 (23.5)	12 (17.1)	28 (20.3)
≥13	52 (76.5)	58 (82.9)	110 (79.7)
Baseline UAS7 score			
Number	68	70	138
Mean (SD)	30.8 (8.2)	31.9 (7.2)	31.3 (7.7)
Median	31.0	32.5	32.0
Q1 ; Q3	24.0 ; 37.5	28.0 ; 37.0	26.0 ; 37.0
Min ; Max	16 ; 42	16 ; 42	16 ; 42
Baseline UAS7 score [n (%)]			
Number	68	70	138
<28	24 (35.3)	17 (24.3)	41 (29.7)
≥28	44 (64.7)	53 (75.7)	97 (70.3)
Baseline HSS7 score			
Number	68	70	138
Mean (SD)	15.0 (4.8)	15.8 (3.8)	15.4 (4.3)
Median	15.5	16.0	16.0
Q1 ; Q3	10.5 ; 19.5	14.0 ; 19.0	12.0 ; 19.0
Min ; Max	2 ; 21	8 ; 21	2 ; 21
Presence of angioedema at baseline[a] [n (%)]			
Number	68	70	138
Yes	34 (50.0)	28 (40.0)	62 (44.9)
No	34 (50.0)	42 (60.0)	76 (55.1)
Baseline AAS7 score for participants with angioedema[a]			
Number	34	28	62

	Placebo (N=68)	Dupilumab (N=70)	All (N=138)
Mean (SD)	35.3 (27.4)	32.1 (23.2)	33.9 (25.4)
Median	28.0	33.5	31.5
Q1 ; Q3	14.0 ; 53.0	9.5 ; 48.0	13.0 ; 48.0
Min ; Max	4 ; 95	4 ; 92	4 ; 95
Baseline UCT score			
Number	68	69	137
Mean (SD)	3.6 (2.3)	3.8 (2.3)	3.7 (2.3)
Median	3.5	4.0	4.0
Q1 ; Q3	2.0 ; 5.0	2.0 ; 5.0	2.0 ; 5.0
Min ; Max	0 ; 9	0 ; 10	0 ; 10
Baseline DLQI score[b]			
Number	67	66	133
Mean (SD)	15.3 (6.7)	13.5 (5.9)	14.4 (6.4)
Median	16.0	13.0	14.0
Q1 ; Q3	10.0 ; 20.0	10.0 ; 18.0	10.0 ; 20.0
Min ; Max	2 ; 28	2 ; 27	2 ; 28
Baseline CU-Q2oL score			
Number	68	69	137
Mean (SD)	46.7 (20.3)	41.0 (17.3)	43.9 (19.0)
Median	45.7	38.0	41.3
Q1 ; Q3	31.0 ; 60.9	27.2 ; 52.2	29.3 ; 57.6
Min ; Max	11 ; 84	12 ; 85	11 ; 85
Baseline PGIS score			
Number	68	70	138
Mean (SD)	3.5 (0.6)	3.4 (0.6)	3.4 (0.6)
Median	3.0	3.0	3.0
Q1 ; Q3	3.0 ; 4.0	3.0 ; 4.0	3.0 ; 4.0
Min ; Max	2 ; 4	1 ; 4	1 ; 4
Baseline Total IgE (IU/mL)			
Number	65	66	131
Mean (SD)	442.3 (1851.8)	636.8 (2886.3)	540.3 (2421.4)
Median	96.5	109.4	101.0
Q1 ; Q3	27.9 ; 221.0	49.2 ; 381.0	38.9 ; 274.0
Min ; Max	1 ; 14827	5 ; 23388	1 ; 23388
Baseline Total IgE (IU/mL) [n (%)]			
Number	65	66	131
<100	34 (52.3)	31 (47.0)	65 (49.6)
≥100	31 (47.7)	35 (53.0)	66 (50.4)
Baseline H1-antihistamines [n (%)]			
Number	68	70	138
standard dose	41 (60.3)	31 (44.3)	72 (52.2)
2-3-fold standard dose	16 (23.5)	27 (38.6)	43 (31.2)
4-fold standard dose	11 (16.2)	12 (17.1)	23 (16.7)

ISS7: itch-severity score over 7 days (0-21); UAS7: urticaria activity score over 7 days (0-42); HSS7: hives-severity score over 7 days (0-21); AAS7: angioedema activity score over 7 days (0-105); UCT: urticaria control test (0-16); DLQI/CDLQI: Dermatology Quality of Life/Children's Dermatology Quality of Life (0-30); PGIS: Patient Global Impression of Severity (1-4); CU-Q2oL: chronic urticaria quality of life questionnaire (0-100)

	Placebo (N=68)	Dupilumab (N=70)	All (N=138)

a Participants with an AAS7 baseline score > 0

b Excludes adolescents/children who completed the CDLQI, 1 adult who incorrectly completed the CDLQI, and 1 child who incorrectly completed the DLQI

PGM=PRODOPS/SAR231893/EFC16461/CSR A3/REPORT/PGM/dem disease r t.sas
OUT=REPORT/OUTPUT/dem_disease_intext_r_t_i.rtf (04MAR2022 7:53)

Medical history and concurrent illnesses

The most common predefined medical history was angioedema, reported in 52.2% of participants overall. Other common predefined medical histories (in >10% of participants overall) included allergic rhinitis (29.0%), asthma (15.2%), and allergic conjunctivitis (10.1%). As required by protocol eligibility criteria, no participants had active AD at study entry; although 5.8% of participants had previous history of AD. There were 8 participants with medical history of CSU associated autoimmune disorders such as autoimmune thyroiditis (6 [4.3%] participants), and Basedow's (Grave's) disease (2 [1.4%] participants).

Prior and concomitant medications

The prior medications used for CSU, including H1-antihistamines and oral corticosteroids (OCS), were balanced between intervention groups. The most commonly used H1-antihistamine was cetirizine/cetirizine hydrochloride (58.7%), and the most commonly used OCS was prednisone (7.2%).

No participants had omalizumab as prior medication, as per inclusion criteria I 07 for this study. One participant had prior exposure to ligelizumab (an experimental anti-IgE agent) more than 3 years before entering this study. During the study, 5 participants (3 in the dupilumab group and 2 in the placebo group) received omalizumab which was prohibited per protocol.

At baseline, all participants were receiving H1-antihistamines for CSU, with 52.2% on standard dose, 31.2% on 2- to 3-fold of standard dose, and 16.7% on 4-fold of standard dose.

Numbers analysed

All randomized participants (n= 138; dupilumab: 70; placebo: 68) were included in the final efficacy population (ITT population).

2.4.2.4.1. Outcomes and estimation

A summary of results for the primary and secondary endpoints in Study A is provided below.

Table 33. Summary of the primary and secondary endpoints in the hierarchical testing procedure - ITT population – EFC16461 Study A

Parameter	Placebo[a] (N=68)	Dupilumab[a] (N=70)	Difference (95% CI)[b] for Dupilumab vs. Placebo	P-value[c]
Primary endpoint				
Change from baseline in UAS7 at Week 24	-12.00 (1.81)	-20.53 (1.76)	-8.53 (-13.16, -3.90)	**0.0003**
Secondary endpoints				
Change from baseline in ISS7 at Week 24	-6.01 (0.94)	-10.24 (0.91)	-4.23 (-6.63, -1.84)	**0.0005**
Proportion of participants with UAS7 ≤ 6 at Week 24	16 (23.5)	32 (45.7)	2.848 (1.301, 6.234)	**0.0075**
Proportion of participants with UAS7 = 0 at Week 24	9 (13.2)	22 (31.4)	2.908 (1.173, 7.209)	**0.0199**
Change from baseline in HSS7 at Week 24	-5.90 (0.93)	-10.28 (0.91)	-4.38 (-6.78, -1.98)	**0.0003**

Parameter	Placebo[a] (N=68)	Dupilumab[a] (N=70)	Difference (95% CI)[b] for Dupilumab vs. Placebo	P-value[c]
Change from baseline in ISS7 at Week 12	-6.01 (0.85)	-8.37 (0.84)	-2.37 (-4.60, -0.13)	**0.0377**
Change from baseline in UAS7 at Week 12	-11.79 (1.64)	-16.81 (1.62)	-5.02 (-9.32, -0.72)	**0.0223**
Proportion of participants with UAS7 ≤ 6 at Week 12	12 (17.6)	24 (34.3)	2.645 (1.154, 6.061)	**0.0215**
Proportion of participants with MID (ISS7 ≥ 5) response at Week 24	29 (42.6)	51 (72.9)	3.413 (1.596, 7.299)	**0.0014**
Proportion of participants with MID (ISS7 ≥ 5) response at Week 12	36 (52.9)	49 (70.0)	1.872 (0.893, 3.923)	0.0971
Change from baseline in HSS7 at Week 12	-5.69 (0.83)	-8.39 (0.83)	-2.70 (-4.90, -0.50)	0.0160
Proportion of participants with UAS7 = 0 at Week 12	6 (8.8)	11 (15.7)	1.970 (0.676, 5.743)	0.2152
Change from baseline in UCT at Week 24	4.88 (0.61)	7.71 (0.59)	2.84 (1.27, 4.40)	0.0004
Change from baseline in UCT at Week 12	4.62 (0.57)	6.48 (0.57)	1.86 (0.35, 3.36)	0.0155

CMH: Cochran-Mantel Haenszel; ISS7: itch-severity score over 7 days (0-21); UAS7: urticaria activity score over 7 days (0-42); HSS7: hives-severity score over 7 days (0-21); UCT: urticaria control test (0-16)

a Values presented are LS mean change from baseline for continuous variables and number and percent of responders for binary variables

b Difference is LS mean difference for continuous variables and CMH odds ratio for binary variables

c All values in bold font are statistically significant according to the hierarchical testing procedure

PGM=PRODOPS/SAR231893/EFC16461/CSR_A3/EXPLO/PGM/eff_hierarchy_test_eu_i_t.sas
OUT=EXPLO/OUTPUT/eff_hierarchy_test_eu_i_t_i.rtf (08FEB2023 2:13)

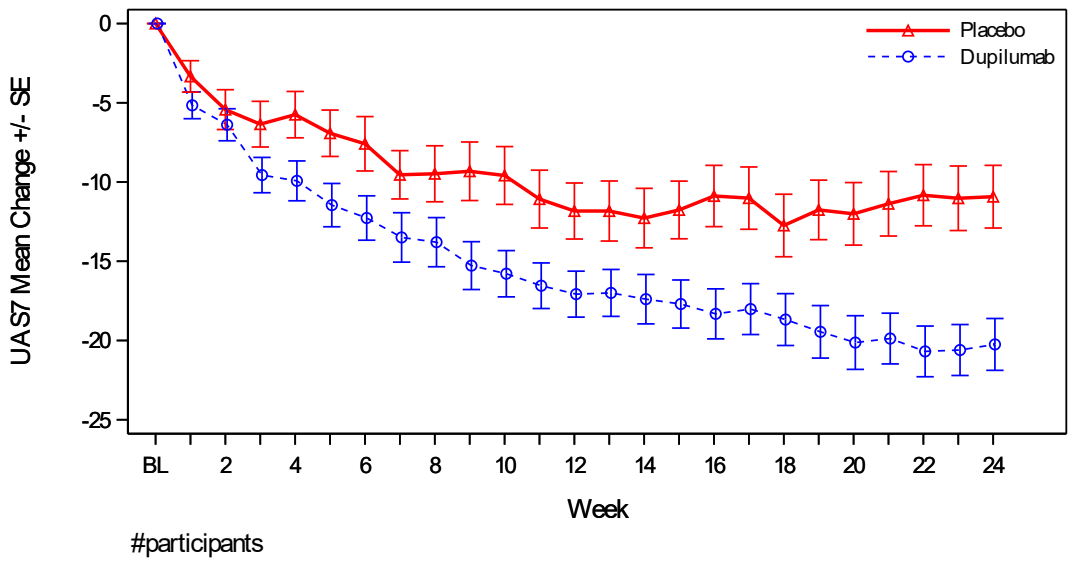
Primary efficacy endpoint

Change from baseline in UAS7 at Week 24

The LS mean change from baseline in UAS7 at Week 24 was -20.53 in the dupilumab group versus -12.00 in the placebo group with a LS mean difference of -8.53 (95% CI: -13.16, -3.90; p=0.0003).

In the dupilumab group, the mean (SD) UAS7 score improved from a severe activity score of 31.86 (7.18) at baseline to mild urticaria status (11.54 [12.22]) at Week 24. In comparison, the mean (SD) UAS7 score in the placebo group decreased from severe (30.76 [8.19]) at baseline to 19.75 (14.58) at Week 24, reaching moderate urticaria activity status.

Figure 33. Plot of mean change from baseline in UAS7 over time during the 24-week treatment period - ITT population – EFC16461 Study A



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Supportive analyses

Proportion of participants with UAS7≤6 at Week 24

At Week 24, 45.7% of participants in the dupilumab group had their CSU symptoms well controlled (UAS7 ≤6) compared with 23.5% in the placebo group, with a statistically significant odds ratio (OR) versus placebo (95% CI) of 2.848 (1.301, 6.234); p = 0.0075.

Proportion of participants with UAS7=0 at Week 24

At Week 24, 31.4% of participants in the dupilumab group versus 13.2% in the placebo group achieved complete resolution of CSU symptoms (UAS7 = 0) with an OR versus placebo of 2.908 (95% CI: 1.173, 7.209; p = 0.0199).

Post-hoc categorical improvement in urticaria activity severity from baseline

In the dupilumab group with severe urticaria activity at baseline, most of the participants, 83.7% (41 out of 49) had a reduced urticaria activity at Week 24. Of them, 34.7% achieved complete resolution of symptoms (defined as UAS7=0). In comparison, for participants in the placebo group with severe urticaria activity at baseline, 54.1% (20 out of 37) had a reduced urticaria activity at Week 24 with only 16.2% achieving complete resolution.

Table 34. Shift table of UAS7 scores from baseline to Week 24 - ITT population– EFC16461 Study A

Baseline UAS7 score	Week 24 UAS7 score	Placebo (N=68)	Dupilumab (N=70)
Moderate (≥16 and <28) (N=41)	Complete/Well-Controlled (≤6)	8/21 (38.1)	10/17 (58.8)
	Complete Control (0)	3/21 (14.3)	5/17 (29.4)
	Well-Controlled (>0 and ≤6)	5/21 (23.8)	5/17 (29.4)
	Mild (>6 and <16)	3/21 (14.3)	3/17 (17.6)
	Moderate (≥16 and <28)	4/21 (19.0)	2/17 (11.8)
	Severe (≥28)	6/21 (28.6)	2/17 (11.8)
Severe (≥28) (N=97)	Complete/Well-Controlled (≤6)	8/37 (21.6)	22/49 (44.9)
	Complete Control (0)	6/37 (16.2)	17/49 (34.7)
	Well-Controlled (>0 and ≤6)	2/37 (5.4)	5/49 (10.2)
	Mild (>6 and <16)	7/37 (18.9)	9/49 (18.4)
	Moderate (≥16 and <28)	5/37 (13.5)	10/49 (20.4)
	Severe (≥28)	17/37 (45.9)	8/49 (16.3)

WOCF: Worst observation carried forward

Note: Data collected after study intervention discontinuation were included. Data post select prohibited/rescue medications were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF.

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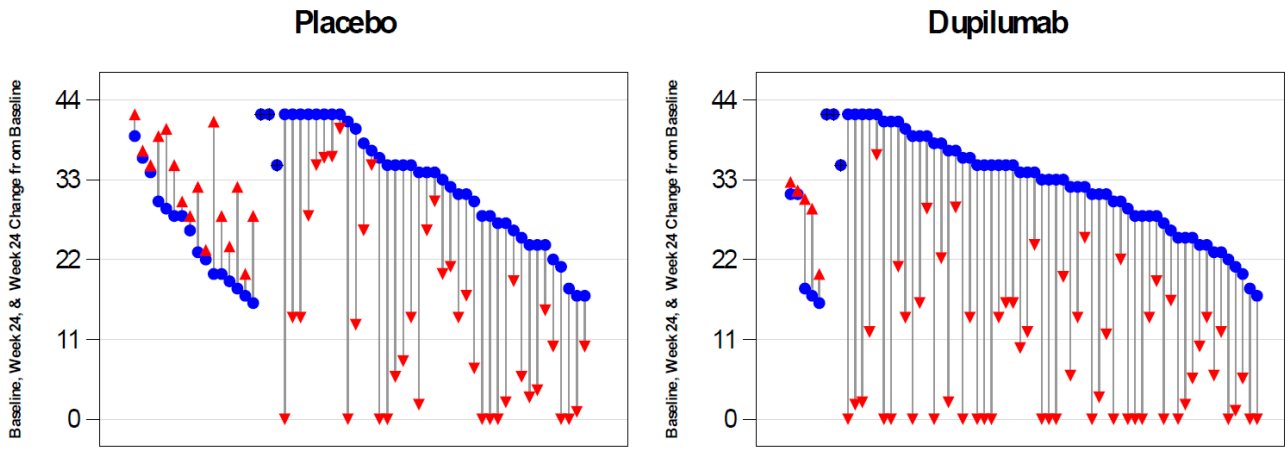
Figure 34. Waterfall plot of UAS7 at Week 24 by treatment group - ITT population – EFC16461 Study A



Post-hoc cumulative probability function analysis

Using an anchor-based approach (PGIS as the anchor), a series of CMTs have been defined in the specific context of use in Study A (Section 1.2.4.6), the estimated CMTs for UAS7 were 16.87 to 21.75 point improvement for within-patient differences and 12.31 to 16.17 point improvements for between-group differences. Approximately 20-25% greater respondents are noted in the dupilumab group across the range of CMTs defined in the specific context of use in Study A. Using ≥22-point improvement in UAS7 as a responder threshold, 48.5% dupilumab-treated patients achieved this threshold versus 25.9% of the placebo group.

Post-hoc between-group difference

The UAS7 treatment difference of -8.53 (95% CI: -13.16, -3.90) was below the absolute CMTs 12.31 to 16.17 between-group difference.

Secondary efficacy endpoints

Change from baseline in ISS7 at Week 24

The LS mean change from baseline in ISS7 at Week 24 was -10.24 in the dupilumab group versus -6.01 in the placebo group; the difference was statistically significant (-4.23, 95% CI: -6.63, -1.84, p=0.0005).

Proportion of ISS7 minimal important difference (MID) (≥5 points) responders at Week 24

A greater proportion of participants with an ISS7 MID response at Week 24 compared with placebo (72.9% versus 42.6%), with an OR versus placebo of 3.413 (95% CI: 1.596, 7.299; p=0.0014) was observed.

Change from baseline in HSS7 at Week 24

The LS mean change from baseline in HSS7 at Week 24 was -10.28 in the dupilumab group versus -5.90 in the placebo group; the difference was statistically significant (LS mean difference versus placebo: -4.38, 95% CI: -6.78, -1.98, p=0.0003).

Change from baseline in UCT at Week 24

The LS mean change from baseline in UCT at Week 24 was 7.71 in the dupilumab group versus 4.88 in the placebo group. A greater increase in UCT was observed in the dupilumab group compared with the

placebo group at Week 24 (LS mean difference: 2.84, nominal p=0.0004). At Week 24, approximately half of participants (34 [48.6%]) treated with dupilumab were well-controlled (UCT≥12) compared to 21 (30.9%) participants treated with placebo.

Angioedema activity score over 7 days (AAS7)

At baseline, only 28 (40%) participants in the dupilumab group and 34 (50%) of participants in the placebo group had active angioedema (AAS7 score >0), with a mean AAS7 score of 32.14 and 35.29, respectively. At Week 24, the LS mean change (decrease) from baseline in AAS7 was -22.51 in the dupilumab group and -23.13 in the placebo group, showing no difference between the two groups.

Treatment effect after study intervention discontinuation

Change from baseline in ISS7 and UAS7 post-treatment

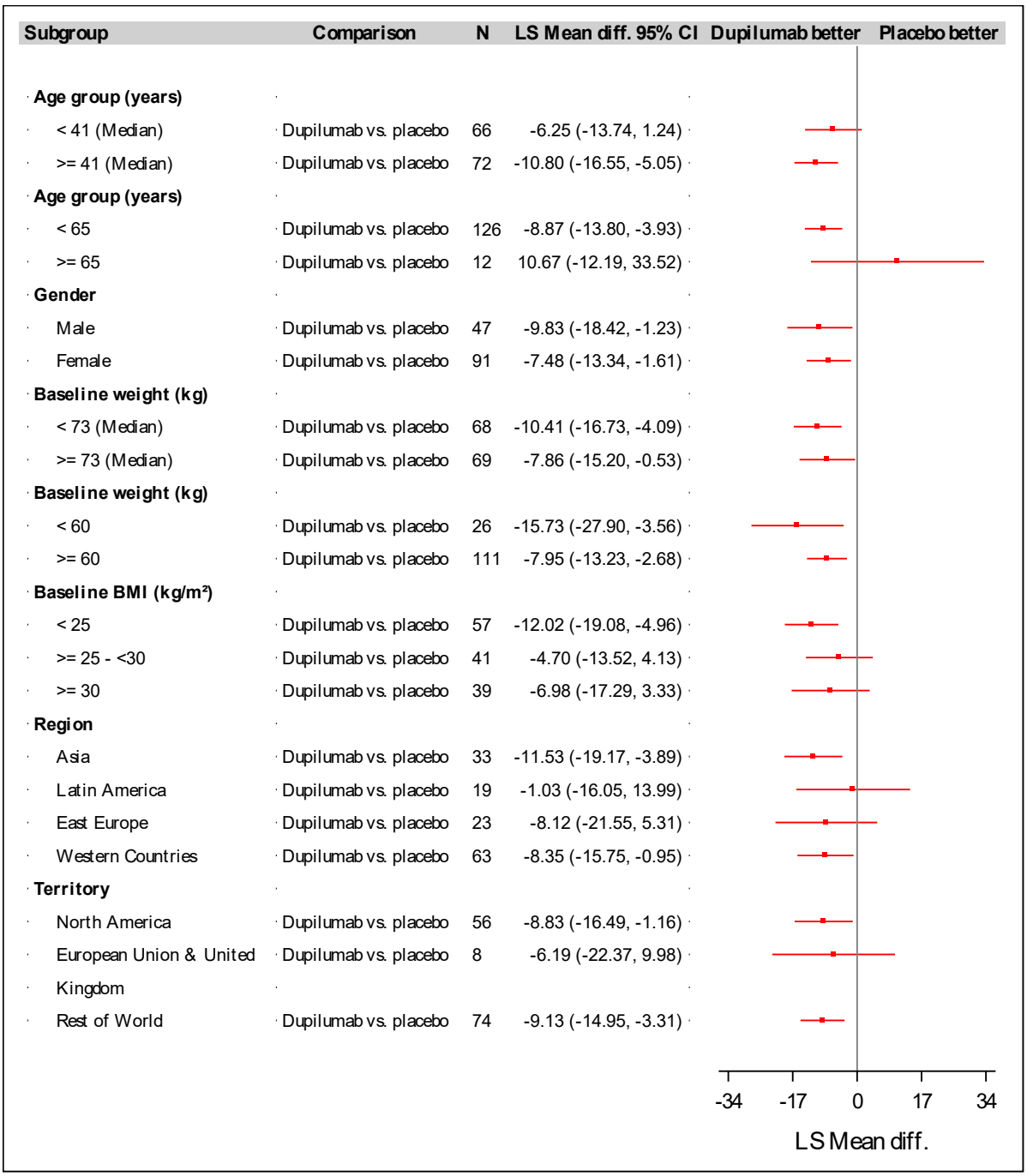
In Study A, a total of 56 participants in the dupilumab group and 51 participants in the placebo group reported post-intervention data at Week 36 for UAS7, ISS7, and HSS7. Post treatment, the mean ISS7 and UAS7 scores in the dupilumab group remained lower compared with the placebo group during the 12-week follow-up period. The mean (SD) UAS7 score in the dupilumab group was 11.54 (12.22) at Week 24 and 13.10 (13.45) at Week 36, compared with 19.75 (14.58) (Week 24) and 18.77 (15.27) (Week 36) in the placebo group. The mean (SD) ISS7 score in the dupilumab group was 5.83 (6.08) at Week 24 and 6.86 (6.97) at Week 36, compared with 10.19 (7.52) (Week 24) and 9.83 (7.97) (Week 36) in the placebo group.

Subgroup analysis

Change from baseline in UAS7 at Week 24 by subgroups

Most subgroups showed a numerically greater treatment effect of dupilumab as compared with placebo in UAS7 reduction at Week 24, except for 1 subgroup (age ≥65 years [N=12]) which had wide confidence intervals with the placebo response higher than in the overall ITT population and the dupilumab response consistent with the overall efficacy results in the ITT population.

Figure 35. Plot of treatment effect on change from baseline in UAS7 at Week 24 by subgroups - ITT population – EFC16461 Study A



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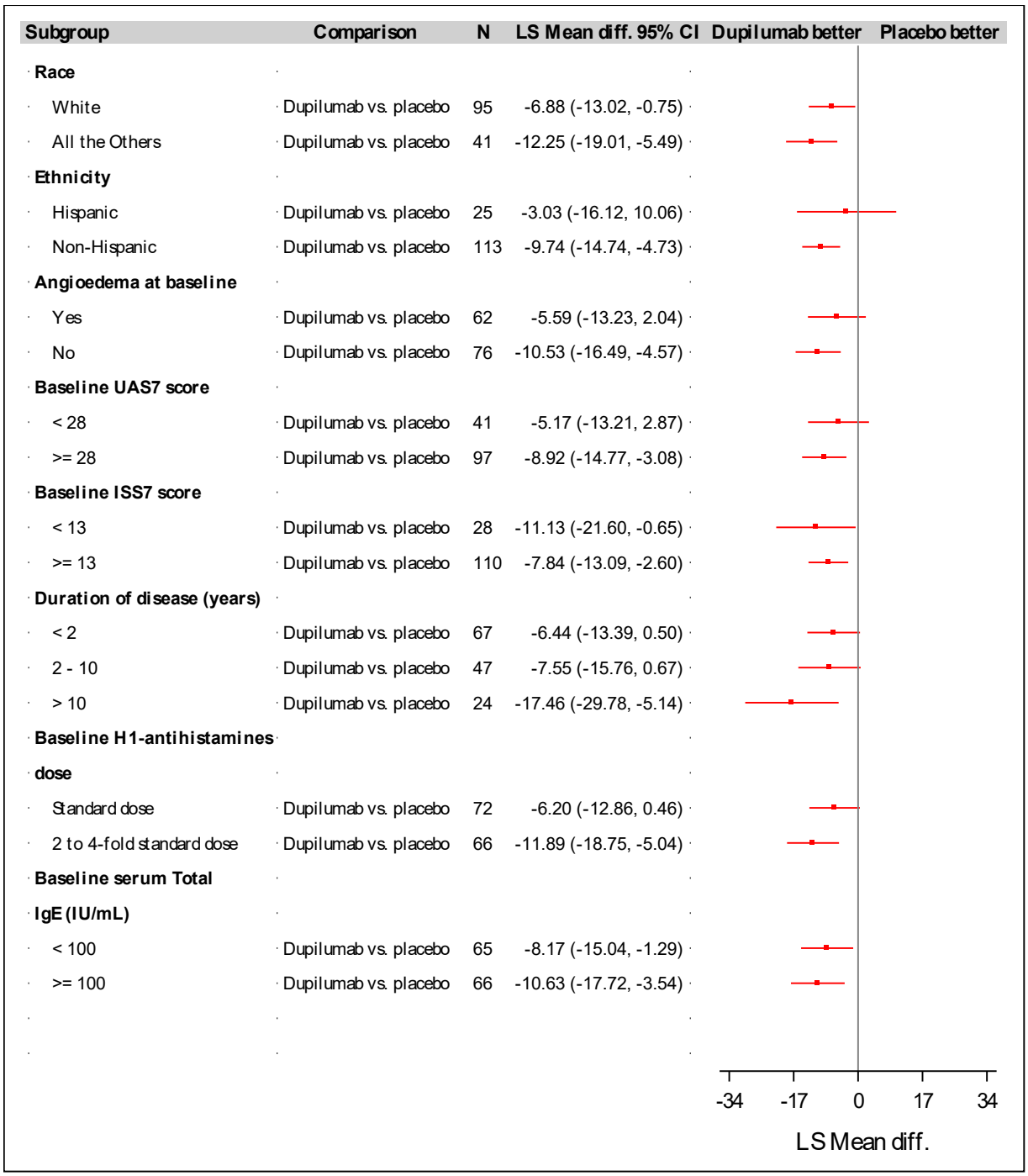

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OUT=REPORT/OUTPUT/eff_ancova_sub_uas7_wk24_2_i_g_i.rtf (14SEP2022 4:04)

Change from baseline in ISS7 at Week 24 by subgroups

Most subgroups showed a numerically greater treatment effect of dupilumab as compared with placebo in ISS7 reduction at Week 24, except for 2 subgroups (age ≥65 years [N=12] and Latin America [N=19]) which had wide confidence intervals with the placebo response higher than in the overall ITT population and the dupilumab response consistent with the overall efficacy results in the ITT population.

Clinical studies in special populations

Efficacy data for adolescents and children (aged ≥6 years and <18 years)

Overall, 6 pediatric participants, 4 adolescents (≥12 to <18 years old) and 2 children ((≥6 to <12 years old) were enrolled in Study A. Efficacy data are shown below.

Table 35. Listing of e-diary data (ISS7, HSS7, UAS7) and questionnaire data (UCT) in adolescents and children - ITT population – EFC16461 Study A

Participant	Intervention group	Age (yrs)/ Sex[a]/ Weight	Timepoint	ISS7	HSS7	UAS7	AAS7	UCT
Adolescents								
Adolescent 1	Placebo	/	Baseline	13	8	21	8	5
			Week 12	0	0	0	0	14
			Week 24	0	0	0	0	15
Adolescent 2	Placebo	/	Baseline	18	18	36	0	7
			Week 12	17.5	12.83	30.33	0	9
Adolescent 3	Dupilumab 200 mg q2w	/	Baseline	14	13	27	0	4
			Week 12	0	0	0	0	12
			Week 24	0	0	0	0	11
Adolescent 4	Dupilumab 300 mg q2w	/	Baseline	20	20	40	0	5
			Week 12	18.67	19.83	38.5	0	10
			Week 24	7[b]	7[b]	14[b]	0[b]	13
Children								
Patient 1	Dupilumab 200 mg q2w	/	Baseline	8	8	16	0	2
			Week 12	7	7	14	0	2
Patient 2	Dupilumab 200 mg q2w	/	Baseline	14	17	31	9	10
			Week 6[c]	7	21	28	0	-

ISS7: itch-severity score over 7 days (0-21); UAS7: urticaria activity score over 7 days (0-42); HSS7: hives-severity score over 7 days (0-21); AAS7: angioedema activity score over 7 days (0-105); UCT: urticaria control test (0-16).

a M=Male, F=Female.

b Assessment collected after end of study intervention date

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

Extracted from: PGM=PRODOPS/SAR231893/EFC16461/CSR_A3/REPORT/PGM/eff_diary_adochild_i_l.sas OUT=REPORT/OUTPUT/eff_diary_adochild_i_l_x.rtf (07MAR2022 3:01)
and PGM=PRODOPS/SAR231893/EFC16461/CSR_A3/REPORT/PGM/eff_qs_adochild_i_l.sas OUT=REPORT/OUTPUT/eff_qs_adochild_i_l_x.rtf (07MAR2022 3:02)

2.4.2.5. Analysis performed across trials (pooled analyses)

Limited Combined Analysis of Study B and Study A IgE <40kU/L subpopulation

Literature suggests that baseline IgE levels below a range of 40-50 kU/L as predictive of incomplete omalizumab response. Hence, a subset of Study A with baseline IgE levels <40 kU/L could be indicative of the population that may be incomplete responders to omalizumab (Study B eligible

population) in this omalizumab naïve population. To support the analysis of dupilumab efficacy in omalizumab incomplete responders, the MAH conducted a limited combined analysis of Study B with Study A based on baseline IgE <40 kU/L.

Table 36. Summary of the primary and select secondary endpoints in the hierarchical testing procedure – EFC16461 Study B ITT population and Combined EFC16461 Study A ITT with baseline IgE <40 kU/L and EFC16461 Study B ITT population

Parameter	Study B ONLY (N=108)				Study B plus Study A Baseline IgE <40 kU/L (N=141)			
	Placebo[a] (N=54)	Dupilumab[a] (N=54)	Difference (95% CI)[b] for Dupilumab vs. Placebo	P-value[c]	Placebo[a] (N=76)	Dupilumab[a] (N=65)	Difference (95% CI)[b] for Dupilumab vs. Placebo	P-value[d]
Primary endpoint								
Change from baseline in UAS7 – Week 24	-8.54 (2.14)	-14.37 (2.16)	-5.83 (-11.37, -0.30)	0.0390	-10.36 (1.90)	-16.33 (2.15)	-5.97 (-10.88, -1.07)	0.0171
Secondary endpoints								
Change from baseline in ISS7 – Week 24	-4.81 (1.08)	-7.68 (1.10)	-2.87 (-5.68, -0.07)	0.0449	-5.46 (0.97)	-8.68 (1.10)	-3.22 (-5.73, -0.72)	0.0117
Change from baseline in HSS7 – Week 24	-3.63 (1.11)	-6.64 (1.11)	-3.01 (-5.88, -0.14)	0.0397	-4.71 (0.97)	-7.70 (1.10)	-2.99 (-5.48, -0.49)	0.0190

CI: Confidence Interval; ISS7: itch-severity score over 7 days (0-21); UAS7: urticaria activity score over 7 days (0-42); HSS7: hives-severity score over 7 days (0-21);
UCT: urticaria control test (0-16)

a Values presented are LS mean change from baseline for continuous variables and number

b Difference is LS mean difference for continuous variables

c Change from baseline in UAS7 – Week 24 in Study B is statistically significant according to the hierarchical testing procedure; others are nominal p-values

d Nominal p-values

Extracted from:

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Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 37. Summary of Efficacy for trial EFC16461 Study A

Title: A randomized, double-blind, placebo-controlled, multi-centre, parallel-group studies of dupilumab in patients with chronic spontaneous urticaria (CSU) show remain symptomatic despite the use of H1 antihistamine treatment in patients naïve to omalizumab **(LIBERTY CSU-CUPID Study A)**			
Study identifier	EFC16461 A EudraCT: 2019-003775-19		
Design	EFC16461 Study A was a 24-week, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of dupilumab in participants with CSU who remained symptomatic despite the use of H1-antihistamine and who were naïve to omalizumab.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Dupilumab		Dupilumab 300 mg Q2W, 52-week treatment period, 70 on dupilumab (67 on 300 mg q2w, 3 on 200 mg q2w)
	Placebo		Matching placebo Q2W, 52-week treatment period, 68 randomized participants
Endpoints and definitions	Primary endpoint	UAS7 at Week 24	Change from baseline in UAS7 at Week 24
	Secondary endpoint	ISS7 at Week 24	Change from baseline in ISS7 at Week 24
	Secondary endpoint	UAS7 ≤ 6 at Week 24	Proportion of participants with UAS7 ≤ 6 at Week 24
	Secondary endpoint	UAS7 = 0 at Week 24	Proportion of participants with UAS7 = 0 at Week 24
	Secondary endpoint	HSS7 at Week 24	Change from baseline in HSS7 at Week 24
	Secondary endpoint	ISS7 at Week 12	Change from baseline in ISS7 at Week 12
	Secondary endpoint	UAS7 at Week 12	Change from baseline in UAS7 at Week 12
	Secondary endpoint	UAS7 ≤ 6 at Week 12	Proportion of participants with UAS7 ≤ 6 at Week 12
	Secondary endpoint	MID at Week 24	Proportion of participants with MID (ISS7 ≥ 5) response at Week 24
	Secondary endpoint	MID at Week 12	Proportion of participants with MID (ISS7 ≥ 5) response at Week 12
	Secondary endpoint	HSS7 at Week 12	Change from baseline in HSS7 at Week 12
	Secondary endpoint	UAS7 = 0 at Week 12	Proportion of participants with UAS7 = 0 at Week 12
	Secondary endpoint	UCT at Week 24	Change from baseline in UCT at Week 24
	Secondary endpoint	UCT at Week 12	Change from baseline in UCT at Week 12
Database lock	05 October 2021		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat population		
Descriptive statistics and estimate variability	Treatment group	Placebo	Dupilumab
	Number of subjects	68	70

	Primary endpoint: Change from baseline in UAS7 at Week 24	-12.00 (1.81)	-20.53 (1.76)
	95% CI	-15.55 to -8.45	-23.99 to -17.08
Effect estimate per comparison	Primary endpoint: Change from baseline in UAS7 at Week 24	Comparison groups	Dupilumab vs Placebo
		Least square means difference (95% CI)	-8.53 (-13.16, -3.90)
		P-value	0.0003
Analysis description	**Secondary Analysis**		
Analysis population and time point description	Intent to treat population		
Descriptive statistics and estimate variability	Treatment group	Placebo	Dupilumab
	Number of subjects	68	70
	Change from baseline in ISS7 at Week 24	-6.01 (0.94)	-10.24 (0.91)
	95% CI	-7.85 to -4.17	-12.03 to -8.46
	Proportion of participants with UAS7 ≤ 6 at Week 24	16 (23.5)	32 (45.7)
	95% CI	14.1 to 35.4	33.7 to 58.1
	Proportion of participants with UAS7 = 0 at Week 24	9 (13.2)	22 (31.4)
	95% CI	6.2 to 23.6	20.9 to 43.6
	Change from baseline in HSS7 at Week 24	-5.90 (0.93)	-10.28 (0.91)
	95% CI	-7.73 to -4.07	-12.07 to -8.49
	Change from baseline in ISS7 at Week 12	-6.01 (0.85)	-8.37 (0.84)
	95% CI	-7.67 to -4.34	-10.03 to -6.72
	Change from baseline in UAS7 at Week 12	-11.79 (1.64)	-16.81 (1.62)
	95% CI	-14.99 to -8.58	-19.99 to -13.62
	Proportion of participants with UAS7 ≤ 6 at Week 12	12 (17.6)	24 (34.3)
	95% CI	9.5 to 28.8	23.3 to 46.6
	Proportion of participants with MID (ISS7 reduction ≥ 5) response at Week 24	29 (42.6)	51 (72.9)
	95% CI	30.7 to 55.2	60.9 to 82.8
	Proportion of participants with MID (ISS7 reduction ≥ 5) response at Week 12	36 (52.9)	49 (70.0)
	95% CI	40.4 to 65.2	57.9 to 80.4

	Change from baseline in HSS7 at Week 12	-5.69 (0.83)	-8.39 (0.83)
	95% CI	-7.32 to -4.05	-10.01 to -6.76
	Proportion of participants with UAS7 = 0 at Week 12	6 (8.8)	11 (15.7)
	95% CI	3.3 to 18.2	8.1 to 26.4
	Change from baseline in UCT at Week 24	4.88 (0.61)	7.71 (0.59)
	95% CI	3.69 to 6.07	6.55 to 8.87
	Change from baseline in UCT at Week 12	4.62 (0.57)	6.48 (0.57)
	95% CI	3.51 to 5.73	5.36 to 7.59
Effect estimate per comparison	Change from baseline in UAS7 at Week 24	Comparison groups	Dupilumab vs Placebo
		Least square means difference (95% CI)	-4.23 (-6.63, -1.84)
		P-value	0.0005
	Proportion of participants with UAS7 ≤ 6 at Week 24	Odds ratio (95% CI)	2.848 (1.301, 6.234)
		p-value	0.0075
	Proportion of participants with UAS7 = 0 at Week 24	Odds ratio (95% CI)	2.908 (1.173, 7.209)
		p-value	0.0199
	Change from baseline in HSS7 at Week 24	Least square means difference (95% CI)	-4.38 (-6.78, -1.98)
		p-value	0.0003
	Change from baseline in ISS7 at Week 12	Least square means difference (95% CI)	-2.37 (-4.60, -0.13)
		p-value	0.0377
	Change from baseline in UAS7 at Week 12	Least square means difference (95% CI)	-5.02 (-9.32, -0.72)
		p-value	0.0223
	Proportion of participants with UAS7 ≤ 6 at Week 12	Odds ratio (95% CI)	2.645 (1.154, 6.061)
		p-value	0.0215
	Proportion of participants with MID (ISS7 reduction ≥ 5) response at Week 24	Odds ratio (95% CI)	3.413 (1.596, 7.299)
		p-value	0.0014
	Proportion of participants with MID (ISS7 reduction ≥ 5) response at Week 12	Odds ratio (95% CI)	1.872 (0.893, 3.923)
		p-value	0.0971
	Change from baseline in HSS7 at Week 12	Least square means difference (95% CI)	-2.70 (-4.90, -0.50)
		p-value	0.0160

	Proportion of participants with UAS7 = 0 at Week 12	Odds ratio (95% CI)	1.970 (0.676, 5.743)
		p-value	0.2152
	Change from baseline in UCT at Week 24	Least square means difference (95% CI)	2.84 (1.27, 4.40)
		p-value	0.0004
	Change from baseline in UCT at Week 12	Least square means difference (95% CI)	1.86 (0.35, 3.36)
		p-value	0.0155

2.4.3. Discussion on clinical efficacy

Data for clinical efficacy is based on the single pivotal **Study B** and a supportive **Study A** conducted in two subsets of CSU patients. Both studies were similarly designed phase 3 studies; multinational, multicenter, randomized, parallel-group, double-blind, placebo-controlled studies with a 24-week treatment and a 12-week follow-up period that were conducted under one master protocol (**EFC16461**). Both studies mainly differed in the study populations enrolled, being intolerant or incomplete responders to omalizumab in Study B or omalizumab naïve patients in Study A. The study population of Study B represents the applicant's sought indication.

For both studies, depending on the participants weight dupilumab 300 mg q2w or dupilumab 200 mg q2w, were compared in adult and adolescent patients (≥12 to <18 years of age) with placebo treatment. This is the same dose regimen as currently approved for atopic dermatitis (see PK/PD assessment in 5.3 for further details).

Design and conduct of clinical studies

Study B and A

Study populations

Study B enrolled adult and adolescent patients aged ≥12 to <18 years with CSU who were symptomatic despite the use of H1-antihistamines and who were inadequate responders or intolerant to anti-IgE therapy while Study A included patients who were refractory to antihistamine treatment but naïve to omalizumab. The diagnosis of CSU had to be confirmed at least 6 months prior to screening with active CSU symptoms (presence of itch and hives) for a minimum of 6 consecutive weeks under antihistamine therapy. Patients had to present with at least moderate urticaria activity (UAS7 ≥16) together with a corresponding ISS7 score of ≥8.

In both studies, participants had to have a history of inadequate response to antihistamines as defined by presence of CSU symptoms for at least 6 weeks at any time prior to screening without any requirement to the antihistamine dose. Participants continued their established standard of care background therapy with long-acting non-sedating H1-antihistamines during the study. Dose adaptations before screening were allowed if doses were stable for at least 3 consecutive days prior to screening. As clarified by the MAH during the procedure, the number of participants with dose adaptions prior to entry of the study was low (n=3).

In Study B, incomplete responders to omalizumab were defined as being treated for CSU with at least 300 mg (q4w) of omalizumab for a minimum of 3 months and showing an inadequate response as per Investigator's assessment. Based on the data provided it is not possible to define the patient population in more detail by means of the nature of the incomplete response to omalizumab. Whether

patients with a complete or only a partial non-response to omalizumab respond differentially to the treatment with dupilumab cannot be evaluated.

Primary endpoints

In both studies, the change from baseline in the weekly urticarial activity score (UAS7) at Week 24 was used as primary endpoint. Of note, with amendment 02, the primary endpoint for the EU and EU reference countries was switched from ISS7 to UAS7 based on the recommendations by CHMP due to the ability of the UAS7 to capture both key symptoms of urticaria, itch and hives.

Secondary endpoints included the change from baseline in the UAS7 subscores, ISS7 and HSS7, as well as the ASS7 to capture changes in the angioedema activity over time. Changes in quality of life were evaluated by DLQI or CDLQI in children, respectively.

Study B

Study conduct

In Study B, a total of 137 participants were screened and 108 participants were randomized to treatment (54 in each group). 16 participants (14.8%) discontinued study intervention prior to week 24 (dupilumab: 6; placebo: 10). In the placebo group, 7 participants discontinued treatment due to lack of efficacy compared to 2 participants in the dupilumab group. A total of 92 (85.2%) participants completed the study intervention period.

Study B was conducted during the global COVID-19 pandemic (first patient enrolled: 03 March 2020) without stoppage. Contingency measures in the study conduct (e.g. phone visits, home visits, online meetings etc) were implemented per protocol amendment. Overall, the impact of the COVID-19 pandemic on the efficacy data interpretation can be considered minimal but led to difficulties in enrolment of intolerant or incomplete responders to omalizumab which were the rationale to include an interim analysis with protocol amendment 04. The interim analysis was planned to be conducted when 80 randomized participants of study B would have completed their 24-week treatment period. This accounts for ~80% of the initially planned patients (52 per group). The interim analysis for Study B was conducted with the cut-off date 17 Dec 2022. At this time, week-24 data from 75 patients (dupilumab: 39; placebo: 36) were analysed. The IA met the specified criteria for futility and the sponsor instructed the sites and investigators to organize early end-of-treatment visits on 18 Feb 2022. By the time of futility notification, 25 participants were remaining of whom 1 participant had already discontinued treatment before the interim analysis; 3 participants (dupilumab: 1; placebo: 3) discontinued treatment after the futility announcement. 9 participants had already completed their end of-treatment visit while the remaining 12 participants were scheduled to complete their end-of-treatment visit within one month. As such the sponsor decided to wait for the remaining week 24 data to be obtained and conduct a final analysis when all randomized participants had completed their last study visit (see "results of the interim analysis" below).

Baseline data

The mean age of the participants was 47.7 years with a range of 14 to 79 years, 72.2% were females, and the majority of participants (77.8%) were White. Only 2 adolescent participants (one per each group) were enrolled in Study B. A total of 25.9% of participants were enrolled in the European Union. The majority (80.6%) of participants had a body weight above the 60 kg (mean body weight: 77.68 kg). The mean time since first diagnosis of CSU was 9.1 years (median: 6.6 yrs). The majority of participants had a disease duration prior to the study between 2 and 10 years.

Around 2/3 of participants (69.4%) presented with a severe CSU (UAS7 ≥28) at baseline while the remaining participants had a moderate CSU activity (UAS7 ≥16). A total of 53 (49.1%) participants presented with angioedema at baseline (AAS7 >0).

The majority of participants were included based on incomplete response to omalizumab (96.3%). In 43.5% of participants, the duration of prior omalizumab treatment was less than 6 months, while the other 25 and 31.5 percent received omalizumab for 6 to 12 or >12 months prior to study entry. The mean total IgE at baseline was 223.2 IU/mL and the median total IgE at baseline was 77.0 IU/mL. A total of 12 (11.1%) participants had a medical history of at least 1 CSU-associated autoimmune disorder. There is no information on the number of patients with one of the currently described autoimmune endotypes of CSU (i.e. autoimmune type I CSU mediated by IgE autoantibodies, type II autoimmune CSU mediated by IgG autoantibodies). The MAH clarified that no laboratory markers to define autoimmune CSU endotypes have been collected during the study as these were not performed routinely as standard of care when the study was conducted. It remains unclear whether these patients show a different or the same response to dupilumab as compared to patients with a non-autoimmune CSU endotype.

Study A

Study conduct

Study A was initiated at the same time as Study B but had faster patient recruitment and study conduct due to the less-refractory study population (omalizumab-naïve patients). A total of 183 participants were screened and 138 participants were randomized to treatment (dupilumab: 70; placebo: 68). 24 participants (17.4%) discontinued study intervention prior to week 24 with a higher number of discontinuations in the placebo arm (n=18) as compared to the dupilumab group (n=6). Accordingly, 118 (85.5%) participants completed the whole study period (dupilumab: 63; placebo: 55).

In study A, no interim analysis was performed.

Baseline data

In Study A, baseline demographics were similar as compared to Study B with differences mainly attributable to the less-refractory CSU population enrolled.

The mean (SD) age of the participants was 41.3 (15.5) years with a range of 8 to 77 years, 65.9% were females, and the majority of participants (68.8%) were White. Study A included 4 adolescent participants (2 in each group). Around 2/3 of participants presented with severe CSU symptom as indicated by an UAS7 ≥28, similar to the study population of study B. A total of 62 (44.9%) participants presented with angioedema at baseline (AAS7 >0). As compared to Study B, participants had an overall shorter disease duration (5.7 years vs. 9.1 years). Almost all participants in EFC16461 Study B were diagnosed more than 1 year ago (98.1%) compared to only 70.3% of participants in EFC16461 Study A. Study A participants had lower utilization of high dose antihistamines (47.8% vs. 63.6%). Participants in Study A had higher median baseline total IgE (101 IU/mL vs. 77 IU/mL). Per protocol, all patients received background antihistamine treatment during the study. 52.2% were on standard approved dose, 31.2% on 2- to 3-fold of standard dose, and 16.7% on 4-fold of standard dose. As compared to study B, a higher number of participants received standard dosing, again indicating the less refractory nature of the patient population enrolled in study A.

Efficacy data and additional analyses

Study B

Primary Endpoint

The study met its primary endpoint. At the end of the treatment period (week 24), a reduction in UAS7 (LS mean decrease from baseline) was observed in both treatment arms (dupilumab: -14.37; placebo: -8.54) with a LS mean difference of -5.83 (95% CI: -11.37, -0.30) that reached statistical significance (p=0.0390). Improvements in UAS7 started to appear early with similar differences between dupilumab and placebo already observed at Week 12 (LS mean difference: -5.11 (95%CI: -10.08, -0.13; nominal p= 0.0443). A 10-point change which is the currently established MID for change in UAS7 was not reached on a group-level which can be attributed to an apparent number of participants with improvements in the placebo arm (likely representing spontaneous remissions) and the overall heterogenous response pattern with a distinct number of participants showing substantial or only minor UAS7 improvements but also worsening in symptoms in both groups. This observation is also reflected by similar numbers of participants in the dupilumab and placebo group who achieved disease control (UAS7 ≤6) or complete resolution in CSU symptoms (UAS7=0) (evaluated as secondary endpoints) with only a slight numerical increase in the dupilumab group. Overall, the results for the primary endpoint do not clearly demonstrate a clinically meaningful difference in UAS7 on a group-level as compared to placebo.

Several post-hoc analysis were performed by the applicant to further compare the numbers of responding patients with meaningful symptom improvements. The post-hoc analysis showed that participants who had at least a 2-category improvement from a severe symptomatic CSU at baseline to mild or to well or complete controlled (reflecting an individual change in UAS7 of more than 12 points) was increased in the dupilumab group (56.7% vs. 27.3%). In addition, there was a higher number of responders with improvements from baseline in UAS7 of ≥7 (64.7% vs. 41.7%) or ≥18 (45.1% vs. 29.2 %) in the dupilumab group.

Overall, it is recognized that on a patient-level the number of participants with meaningful UAS7 improvements was increased in dupilumab-treated participants. However, given the post-hoc nature of the responder analysis, the statistical strength is limited. Moreover, the results also strongly indicate that a considerable number of participants did not receive additional benefit with dupilumab as compared to placebo and improvements may in part be attributable to the self-limiting nature of the disease.

Secondary Endpoints

Similar changes in ISS7 and HSS7 as for UAS7 were observed at week 24 indicating that the improvements in urticarial symptoms were driven by both a reduction in itch and reduction in hives. The LS mean difference in ISS7 versus placebo at week 24 was -2.87 (95% CI: -5.68, -0.07; p= 0.0449). slightly missing the specified threshold of p<0.0430 which was lowered to the performed interim analysis. The LS mean difference in HSS7 versus placebo at week 24 was -3.01, (95% CI: -5.88, -0.14, nominal p=0.0397). As for the primary endpoint, for both, changes in ISS7 and HSS7, a clear meaningful difference could not be demonstrated on a group level. Still, on a patient-level, higher numbers of participants with improvements above the literature-derived MID (5-point change) as well as above the post-hoc anchor-based derived thresholds (ISS7: 7.00 to 10.50; HSS7 6.38 to 8.00) was observed.

Consistent with the higher number of participants with UAS7 improvements, a higher number of participants with UCT >12 (well-controlled) was observed in the dupilumab group (44.4% vs. 20.4%). The median UCT score in dupilumab group differed between placebo (11.0 vs. 7.5) but was below 12 points again indicating the overall heterogenous treatment response. Similar improvements in the angioedema activity score were observed for both dupilumab and placebo with no difference between the groups (-16.29 vs. -16.54). The limited improvements seen on a group-level for the patient-

reported primary endpoint (UAS7) were also reflected in changes observed for the other patient-reported outcome measures CU-Q2oL, PGIC/PGIS and DLQI.

Results of the interim analysis

As outcome of the interim analysis, the LS mean difference for UAS7 was -3.15 (95%CI: -9.79, 3.49; p=0.3529) and -1.96 (95%CI: -5.338, 1.42; p=0.2555) for ISS7, respectively. Consequently, the IA met the pre-specified criteria for futility which was communicated to the investigators and to the public on 18 Feb 2022. As a consequence, 3 participants discontinued study treatment due to the IA announcement, while the remaining 12 participants continued their home-administration of the IMP that was implemented due to the COVID-19 pandemic at this time (2022). These 12 participants all had a regular end-of-treatment visit (with the last visit completed on March 24th, 2022. As stated by the applicant, given the status of the participants not included in the interim analysis of whom a majority had already completed the 24-week visit or had already scheduled an end-of-treatment visit within the next months, the sponsor to conduct a final analysis including all remaining 15 participants.

More details on the process and timelines of the interim analysis were provided during the procedure. By the time of the futility notification (18-Feb-2022), a total of 15 participants were still on treatment. In line with the study protocol which specified that "in the case of futility, study treatment will be stopped for all participants", the applicant recommended investigators to contact and inform participants who were still receiving study treatment upon receipt of this futility notification and organize an early end of treatment (EOT) visit, as appropriate. The treatment was not stopped immediately for these participants and investigators and patients jointly decided whether to continue treatment considering that only a few weeks of treatment were left. Of note, a "limited Sponsor unblinded team" re-analysed the data after the IARC had provided the recommendation to stop the trial for futility on 25 Jan 2022. This took place over a period of more than three weeks. The trial was subsequently stopped by the MAH in line with the protocol. It remains unclear which information was available to the IARC at the time of decision making (e.g. which endpoints, which additional data, which analyses, …), what information was shared with the sponsor in the IARC recommendation, and what analyses were conducted and based on which data (same DBL or updated data cut-off) by the sponsor afterwards. In any case, given that the trial was fully enrolled, follow up was very mature, and the futility criterion was very strict, it is not understandable at all, why the study sponsor followed the recommendation of the IARC to stop the trial. As outlined in the Questions and answers on Data Monitoring Committees issues (EMA/CHMP/470185/2020), DMC recommendations are not binding to the Sponsor and the "ultimate responsibility for a clinical trial rests with the study Sponsor and thus the Sponsor must conclude whether or not to follow DMC recommendations".

Of note, there is a large shift in mean UAS7 reductions in favour of the dupilumab arm in participants that were analysed after the IA (n=24). At the interim analysis, the effect of UAS7 (change from baseline to week 24 versus placebo) was -3.15 (95% CI -9.79, 3.49). This result was based on n = 83 patients. At the primary analysis, with n = 108 patients, the result nearly doubled to -5.83 (95% CI -11.37, -0.30). While this indeed might show that there was no (strong) bias induced by the announcement of interim results and the plan to stop the trial for futility, it also shows that the results are very volatile and change substantially by adding only 25 subjects (23% of all enrolled patients). Given the need for compelling results (see below) in this single pivotal trial setting this is seen very critical. It rather shows that the treatment has a small effect and is very variable.

As the futility analysis was non-binding, from a technical perspective no type 1 error inflation occurred and in principle adequate type 1 error control was in place at both analyses. However, given that the decision was made to stop the study for futility, it is not considered possible to revert this decision and to consider the study successful after the fact. The trial was considered negative by the Sponsor and this was communicated via a press release and to trial participants. This decision cannot be ignored or

overruled. However, despite a (formally) negative trial, one can decide to apply for the claimed indication based on the trial. In that case, it is paramount that trial results are especially compelling and robust.

The results of Study B are, however, not able to fulfil this requirement. As described before, a clinical meaningful treatment effect has not been clearly observed on a group-level. On a patient-level, data suggest that meaningful symptom improvement have been achieved after treatment with dupilumab in a subset of patients but these results are limited due to the post-hoc nature of the analysis. The overall limited clinical response might be partially explained by the heterogenous response pattern with a distinct number of patients also improving under placebo treatment, reflecting the spontaneous and in part self-limiting nature of the disease. As there is no independent support from a second trial in the same CSU patient population a clear demonstration of efficacy cannot be concluded from this data.

Study A

Primary Endpoint

The study met its primary endpoint. At week 24, reductions in UAS7 (LS mean decrease from baseline) were -20.53 in the dupilumab group and -12.00 in the placebo group, respectively. The LS mean difference was -8.53 (95% CI: -13.16, -3.90). Statistical significance was reached (p=0.0003). Improvements in UAS7 started to appear early. Change from baseline in UAS7 at Week 12 were -16.81 and -11.79 in the dupilmab and placebo group, respectively, with a LS mean difference of -5.02 (95%CI: -9.32, -0.72; p=0.0223). Still, the largest mean differences between dupilumab and placebo were only achieved after >Week 20, indicating that the maximal clinical response was achieved near the end of the 24-week study treatment period. Whether patients might have shown further improvements beyond 24-week was not evaluated.

Overall, substantial greater categorial responses and greater numbers of individual UAS7 improvements were seen in omalizumab naïve patients in Study A. Disease control (UAS7 ≤6) or complete resolution of CSU symptoms (UAS7=0), evaluated as secondary endpoint, was achieved in an increased number of participants in the dupilumab group as compared to placebo (45.7% vs. 23.5% and 31.4% vs. 13.2%) with statistically significant differences detected. As observed for incomplete omalizumab responders in Study B, there was also a notable number of placebo responders. Consequently, the LS UAS7 mean difference closely missed the established MID (10-point change).

Secondary Endpoints

As observed in Study B, improvements in urticarial symptoms were similarly driven by reductions in both, itch and hives.

The LS mean difference in ISS7 versus placebo at week 24 was -4.23 (95% CI: -6.63, -1.84, p=0.0005). The LS mean difference in HSS7 versus placebo at week 24 was -4.38, (95% CI: -6.78, -1.98, p=0.0003). For both secondary endpoints, LS mean group differences were slightly below the established MIDs (5-point change). Of note, the proportion of participants with an ISS7 MID response at Week 24 was 72.9% vs 42.6% in the placebo group (95% CI: 1.596, 7.299; p=0.0014). At Week 24, approximately half of participants (34 [48.6%]) treated with dupilumab were well-controlled (UCT≥12) compared to 21 (30.9%) participants treated with placebo. As also seen within Study B, improvements in angioedema were seen for both groups with no difference observed (-22.51 vs. -23.13).

Overall, improvements seen in Study A support the overall effect of dupilumab in CSU while differences in the UAS7 response between Study A and B may be linked to the more refractory disease characteristics of patients with an inadequate omalizumab response. It is unclear whether incomplete

omalizumab responders included in Study B represent a distinct CSU endotype with specific pathological elements. In this regard, recent literature currently discusses whether low IgE baseline levels, indicating IgE-independent or less dependent disease pathology, can be predictive of an incomplete omalizumab response. Still, no precise predictive threshold has been currently established and the provided post-hoc analysis with the complete data from Study B combined with a subpopulation patients from Study A with baseline IgE <40 kU/L is therefore considered of low supportive value.

Additional analyses

Treatment effect after study intervention discontinuation

Patients were treated for only 24 weeks. In both studies, there was no clear loss of response in UAS7 or ISS7 and HSS7 after treatment discontinuation during the 12-week follow-up period while first indications for a worsening in urticarial symptoms appear to emerge in study A. In Study B, no change in difference between placebo and dupilumab is observed at Week 36. Given these data, it is uncertain whether long-term therapy with the proposed posology is needed to maintain improvements in CSU symptoms once a satisfactory clinical response is achieved. The need for continued therapy should be regularly assessed by the prescribing physician. This will be be reflected in the SmPC.

Treatment effect in subgroups

In Study B, most subgroups showed a numerically greater treatment effect of dupilumab as compared with placebo in UAS7 reduction at Week 24. Improvements in UAS7 appear to be related with the duration of disease prior to study entry. The strongest improvements in UAS7 were observed in patients with a short duration of disease while the lowest improvements were seen in patients with long disease duration. Of note, an opposite pattern is observed in Study A.

No clear tendency for a greater difference in UAS7 improvements is seen in participants with IgE levels below 77 IU/ml, in Study B, while a greater treatment effect was seen in patients with higher IgE baseline levels (>77.0 IU/mL). Still, changes from IgE baseline did not correlate with UAS7 improvements.

Results of the subgroup analysis in Study A were mostly consistent with Study B.

Assessment of paediatric data on clinical efficacy

Study B included 2 adolescent participants aged 16 and 14 years. Additionally, Study A included 4 adolescents between 12 and 17 years of age. In both studies, participants were equally randomized to dupilumab and placebo. The included numbers are in line with the PIP. Due to the limited number of adolescents included in study B, no conclusion on the efficacy for participants below 18 years can be made and the approval for the treatment of adolescents relies on the extrapolation of efficacy data obtained in adults to the adolescent CSU population. This approach is considered acceptable as disease pathology can be assumed to be sufficiently similar between adults and adolescents.

2.4.4. Conclusions on the clinical efficacy

The applicant is seeking approval for the treatment of patients with CSU who are symptomatic despite treatment with H1-antihistamines and who are intolerant to or inadequately controlled by anti-IgE therapy. Main efficacy data are derived from the single pivotal study EFC16461 (Study B) that evaluated dupilumab in moderate-to-severe antihistamine refractory CSU patients with a previous incomplete response to omalizumab. Supportive data are derived from study EFC16461 (Study A) that enrolled patients who were omalizumab naïve. Only the study population of Study B represents the

applicant's sought indication. Both studies only included treatment up to 24 weeks. Extrapolation of efficacy from adults to adolescents is acceptable.

The efficacy results indicate that in incomplete omalizumab responders (Study B), despite showing statistical significance for the primary endpoint, a beneficial treatment effect, as seen by improvements in the main urticaria symptoms itch and hives was not clearly demonstrated on a group-level. Overall, the treatment response was heterogeneous with a distinct number of participants showing substantial or only minor UAS7 improvements but also worsening in symptoms in both treatment groups. Additional analysis indicates that numbers of participants with substantial symptom improvements were increased as compared to placebo but these results are limited due to the post-hoc nature of the analysis and are thus not especially compelling. Given the overall heterogenous response characteristics, it can be anticipated that a considerable number of patients may not receive additional benefit with dupilumab.

A major limitation of Study B is the widely diverging results obtained at the interim analysis and thereafter (showing futility first and statistical significance later on) strongly indicating that clinical responses in this patient population are very volatile and can change substantially by adding only 25 subjects (23% of all enrolled patients). Given that the decision was made to stop the study for futility, it is not considered possible to revert this decision and to consider the study successful after the fact. If efficacy is to be claimed based on Study B, the results need to be especially compelling and robust, which, however, was not convincingly demonstrated. Further, there is no independent support from a second trial in the same CSU patient population.

Overall, the treatment effect as observed in the pivotal Study B is considered not sufficiently robust to demonstrate efficacy of dupilumab in the sought indication. (**MO**).

2.5. Clinical safety

2.5.1. Introduction

Indications

Dupilumab is approved in the EU for the following indications:

- Atopic dermatitis (AD)

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 (PN)

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.

Overview of safety database in adults and adolescents

The safety data from placebo-controlled studies of other dupilumab indications approved in 1 or more countries used for comparison of safety profiles across indications and between adults and adolescents were:

• The primary safety pool in the initial **AD** submission in adults: 1047 participants exposed to dupilumab 300 mg q2w or 300 mg qw (R668-AD-1021, R668-AD-1334, and R668-AD-1416, 16-week safety pool). In adolescents with AD: 165 participants exposed to dupilumab q2w tiered by weight (200 mg if body weight <60 kg or 300 mg if body weight ≥60 kg) during 16 weeks in Study R668-AD-1526.

• The primary safety pool in the adults and adolescents with **Asthma**: 1449 adults and 68 adolescents exposed to dupilumab 300 mg q2w or 200 mg q2w (DRI12544, 24-week safety pool, adults only; EFC13579, 52-week safety pool, adults and adolescents).

• The primary safety pool in the adults with **CRSwNP**: 440 participants exposed to dupilumab 300 mg q2w (EFC14146 and EFC14280, 24-week safety pool).

• The primary safety pool in the adults and adolescents with **EoE**: 54 adults and 27 adolescents exposed to dupilumab 300 mg q2w and 108 adults and 37 adolescents exposed to dupilumab 300 mg

qw (R668-EE-1774 Part A and Part B, 24-week treatment period and R668-EE-1324, 12-week treatment period).

• The primary safety pool in the adults with **PN**: 152 participants exposed to dupilumab 300 mg q2w (EFC16460 and EFC16459, 24-week safety pool) Overall, in the completed dupilumab clinical program, the safety profile was acceptable and consistent across approved indications and between adolescents and adults.

Overall, in the completed dupilumab clinical program, the safety profile was acceptable and relatively consistent across approved indications and between adolescents and adults.

Safety Data for CSU - Sources

Main safety data

The safety analyses are based on the results from the two completed Phase 3 studies EFC16461 Study B (108 participants) and EFC16461 Study A (138 participants). A brief description of the 2 studies are provided in Table 38 below.

Table 38. Overview of Phase 3 chronic spontaneous urticaria studies evaluated in the Summary of Clinical Safety

Study number/Status at submission cut-off date	Summary of key study information	Planned study duration	Number of participants evaluated for safety
EFC16461 Study B Completed	A randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in participants with chronic spontaneous urticaria who remain symptomatic despite the use of H1-antihistamine treatment and who are intolerant or incomplete responders to omalizumab. Population: adults, adolescents (aged 12 to <18 years). Dose regimen (SC injection): Adults regardless of body weight and adolescents ≥60 kg: loading dose on Day 1 of 600 mg (2 SC injections of 300 mg) or matching placebo; followed by 300 mg or matching placebo q2w for 24 weeks Adolescents ≥12 to <18 years of age ≥30 to <60 kg: loading dose on Day 1 of 400 mg (2 SC injections of 200 mg) or matching placebo; followed by 200 mg or matching placebo q2w for 24 weeks	36 weeks after randomization (24 weeks of treatment + 12 weeks of follow-up)	108 (54 dupilumab / 54 placebo)
EFC16461 Study A Completed	A randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in participants with chronic spontaneous urticaria who remain symptomatic despite the use of H1-antihistamine treatment and that are naïve to omalizumab. Population: adults, adolescents (aged 12 to <18 years), and children (aged 6 to <12 years). Dose regimen (SC injection): Adults regardless of body weight and adolescents ≥60 kg: loading dose on Day 1 of 600 mg (2 SC injections of 300 mg) or matching placebo; followed by 300 mg or matching placebo q2w for 24 weeks Adolescents and children ≥6 to <12 years of age ≥30 to <60 kg: loading dose on Day 1 of 400 mg (2 SC injections of 200 mg) or matching placebo; followed by 200 mg or matching placebo q2w for 24 weeks Children ≥6 to <12 years of age ≥15 to <30 kg: loading dose on Day 1 of 600 mg (2 SC injections of 300 mg); followed by 300 mg or matching placebo q4w for 24 weeks	36 weeks after randomization (24 weeks of treatment + 12 weeks of follow-up)	138 (70 dupilumab / 68 placebo)

q2w: every 2 weeks, q4w: every 4 weeks, SC: subcutaneous

Supportive safety data

The following additional supportive safety data from other sources are also provided:

• All new SUSARs from ongoing Phase 2/3 and Phase 4 interventional studies received from 01 June 2023 (cut-off date for SUSARs of the most recent marketing application for dupilumab [EoE ≥1 to <12 years]) to 29 September 2023 (SUSARs and deaths cut-off date for the current application).

• Brief safety summary of completed clinical programs in other approved populations (AD, asthma, CRSwNP, EoE, and PN)

• Data from post-marketing surveillance for approved indications.

Overview of the studies

Study B

EFC16461 Study B was a randomized, double-blind, placebo-controlled, parallel group study of dupilumab in adults and adolescents aged 12 to <18 years with CSU intolerant or incomplete responders to omalizumab.

The primary objective was to evaluate the efficacy of dupilumab in comparison to placebo in participants with CSU who remain symptomatic despite the use of H1-antihistamine treatment and who are intolerant or incomplete responders to omalizumab.

The secondary/exploratory objectives of the study relevant to the safety summary were to assess the safety and tolerability of dupilumab in comparison to placebo, its systemic exposure, and incidence of treatment-emergent ADA.

Omalizumab incomplete responders are defined as participants treated SC with at least 300 mg omalizumab q4w for at least 3 months (minimum of 3 injections) and who have had an inadequate response resulting in omalizumab discontinuation, as confirmed by Investigator assessment. Dupilumab or matching placebo was administered SC for 24 weeks according to the regimens described in Table 38.

The study comprised the following periods with a total duration of 38±2 weeks for each participant:

• A screening period (2-4 weeks), during which the suitability of participants to participate in the trial was determined.

• An intervention period (up to 24 weeks) during which the participants received SC dupilumab q2w (or q4w) or matching placebo q2w (or q4w). Participants were randomized to either dupilumab or placebo in a 1:1 ratio.

• A post-treatment period (12 weeks).

A prespecified interim analysis was performed when the first 83 randomized participants had completed or would have completed their Week 24 visit by the interim analysis cut-off date to assess for efficacy at the interim analysis, continue the study, or stop for futility in the ITT24 population. The outcome of this interim analysis met the protocol-specified efficacy statistical criteria for futility.

Study A

EFC16461 Study A was a randomized, double-blind, placebo-controlled, parallel group study of dupilumab in adults, adolescents aged 12 to <18 years, and children aged 6 to <12 years with CSU naïve to omalizumab. The primary and secondary objectives were the same as EFC16461 Study B, except for the participant population which is participants with CSU who remain symptomatic despite the use of H1-antihistamine treatment and who are naïve to omalizumab.

Dupilumab or matching placebo (randomization ratio 1:1) were administered subcutaneously for 24 weeks according to the same adult and adolescent regimens as EFC16461 Study B; in addition, children (aged 6 to <12 years) were eligible with dosing regimen described in Table 38 above. The study comprised the same periods and the same total duration as EFC16461 Study B.

The integrated evaluation of the safety of dupilumab treatment in CSU was based on the pooled data from all treated participants from the completed EFC16461 Study B and EFC16461 Study A

Disposition of study participants

The safety pool comprised 246 participants from EFC16461 Study B and EFC16461 Study A who received either dupilumab (124 participants) or placebo (122 participants) (see Table 39). Among the 246 participants, 206 (83.7%) completed the 24-week intervention period and 40 (16.3%) prematurely discontinued study intervention. Early study intervention discontinuation rate was lower in the dupilumab group compared to the placebo group (12 [9.7%] and 28 [23.0%] participants, respectively).

The main reason for study intervention discontinuation was lack of efficacy (either per the Investigator's judgement or per "Withdrawal by subject" with lack of efficacy as reason), reported more frequently in the placebo group (14 [11.5%] participants) than in the dupilumab group (5 [4.0%] participants). Seven participants discontinued study intervention due to adverse event not related to COVID-19. In 6 participants (2 [1.6%] in the dupilumab group and 4 [3.3%] in the placebo group), the discontinuation was per the Investigator's judgement (see PTs by intervention group in Table 34). A "Withdrawal by subject" occurred in 1 (0.8%) participant in the placebo group who experienced TEAEs of migraine (since Day 1) and somnolence (since Day 16). Overall, 6 adolescents aged ≥12 to <18 years (3 in the dupilumab group and 3 in the placebo group) and 2 children aged ≥6 to <12 years (8 and 10 years old, both in the EFC16461 Study A dupilumab group) were enrolled. One adolescent in the placebo group and both children in the dupilumab group discontinued the study intervention for reasons related to lack of efficacy (1 per Investigator's decision, 2 "Withdrawal by subject").

Table 39. Participant disposition – Pooled safety population

n (%)	Placebo (N=122)	Dupilumab (N=124)	All (N=246)
Randomized and exposed	122 (100)	124 (100)	246 (100)
Completed the study intervention period	94 (77.0)	112 (90.3)	206 (83.7)
Did not complete the study intervention period	28 (23.0)	12 (9.7)	40 (16.3)
Reason for permanent study intervention withdrawal			
Adverse event	4 (3.3)	2 (1.6)	6 (2.4)
Related to COVID-19	0	0	0
Not related to COVID-19	4 (3.3)	2 (1.6)	6 (2.4)
Lack of efficacy	9 (7.4)	3 (2.4)	12 (4.9)
Poor compliance to protocol	1 (0.8)	0	1 (0.4)
Withdrawal by subject	11 (9.0)	5 (4.0)	16 (6.5)
Other	3 (2.5)	2 (1.6)	5 (2.0)
Related to COVID-19	0	0	0
Not related to COVID-19	3 (2.5)	2 (1.6)	5 (2.0)
Reason for study intervention withdrawal by subject[a]			
Adverse event	1 (0.8)	0	1 (0.4)
Related to COVID-19	0	0	0
Not related to COVID-19	1 (0.8)	0	1 (0.4)
Study procedure	0	0	0
Lack of efficacy	5 (4.1)	2 (1.6)	7 (2.8)
Other	5 (4.1)	3 (2.4)	8 (3.3)
Related to COVID-19	0	0	0
Not related to COVID-19	5 (4.1)	3 (2.4)	8 (3.3)

n (%)	Placebo (N=122)	Dupilumab (N=124)	All (N=246)
Completed the study period	102 (83.6)	112 (90.3)	214 (87.0)
Did not complete the study period	20 (16.4)	12 (9.7)	32 (13.0)
Reason for study discontinuation			
Adverse event	3 (2.5)	2 (1.6)	5 (2.0)
Poor compliance to protocol	1 (0.8)	0	1 (0.4)
Withdrawal by subject	13 (10.7)	6 (4.8)	19 (7.7)
Site terminated by sponsor	0	0	0
Study terminated by sponsor	0	0	0
Other	3 (2.5)	4 (3.2)	7 (2.8)
Related to COVID-19	0	0	0
Not related to COVID-19	3 (2.5)	4 (3.2)	7 (2.8)

a This is a further breakdown of the reasons for withdrawal by subject reported above, as collected in the standard CRF form.
Percentages are calculated using the number of participants exposed as denominator
PGM=PRODOPS/SAR231893/OVERALL/ISS_CSU_2021/REPORT/PGM/dis_dispo_s_t.sas
OUT=REPORT/OUTPUT/dis_dispo_s_t_i.rtf (24AUG2022 4:42)

Extent of exposure

Cumulative exposure to study intervention was slightly higher in the dupilumab group (54.2 PY in the dupilumab group and 48.9 PY in the placebo group). The mean (SD) duration of IMP exposure was 159.7 [31.1] days in the dupilumab group and 146.3 [44.4] days in the placebo group, with 76.6% and 67.2% participants exposed for at least 24 weeks to dupilumab or placebo, respectively. The PY

exposure to the study intervention in the pooled safety population, along with the exposure from each study separately is summarized in Table 40.

Table 40. Patient-years exposure to investigational medicinal product by study – Pooled safety population

Studies	Placebo (N=122)	Dupilumab (N=124)
EFC16461-A		
N=exposed	68	70
Patient-years	26.2	30.9
EFC16461-B		
N=exposed	54	54
Patient-years	22.7	23.3
All		
N=exposed	122	124
Patient-years	48.9	54.2

Exposure by subgroup

Given that the majority of participants were 18 to 64 years of age (84.6%), were Caucasian/White (72.8%), and females (68.7%), exposure to study intervention was highest in those categories: 18 to 64 years of age (44.8 PY in the dupilumab group and 42.5 PY in the placebo group); Caucasian/White participants (38.7 PY in the dupilumab group and 35.6 PY in the placebo group) and female participants (33.6 PY in the dupilumab group and 36.9 PY in the placebo group). By region, exposure was highest in Western countries (26.3 PY in the dupilumab group and 23.1 PY in the placebo group). Western countries included Canada, France, Germany, Spain, the United Kingdom, and the US.

Exposure in adolescent participants was 1.4 PY in the dupilumab group and 1.2 PY in the placebo group.

2.5.2. Demographics, Baseline Characteristics, Medical History

Demography

Demographics and participant characteristics at baseline in the pooled safety population were balanced between the 2 intervention groups. The mean (SD) age of the randomized population was 44.1 (16.0) years with a range of 8 to 79 years. The majority of participants were adults aged 18 to 64 years (85%), 6 (2.4%) participants were adolescents (age group 12 to 17 years), and 2 (0.8%) were children (age group 6 to 11 years). There were 30 elderly participants randomized, 24 (9.8%) in the age group 65 to 74 years and 6 (2.4%) in the age group ≥75 years. Overall, 31.3% of participants were male and 68.7% were female. The mean (SD) body weight was 77.01 (19.14) kg, with 19.2% of participants <60 kg and 80.8% of participants ≥60 kg. There were no participants with baseline body weight <30 kg.

Disease characteristics at baseline

Overall, disease characteristics at baseline were balanced between the 2 intervention groups in the pooled safety population. The mean (SD) time since first diagnosis of CSU prior to study entry was 7.2 (8.9) years, the mean (SD) baseline ISS7 score was 16.0 (4.0) (ranging from 8 to 21, with study inclusion criteria ISS7 ≥8). The mean (SD) baseline UAS7 score was 31.4 (7.8) corresponding to severe urticaria activity (ranging from 16 to 42, with inclusion criteria UAS7 ≥16 corresponding to

moderate urticaria activity and 28-42 corresponding to severe urticaria activity). The majority of participants (69.9%) had severe CSU disease activity at baseline with a corresponding baseline UAS7 score ≥28, and the remaining participants had moderate disease activity. The mean (SD) UCT at baseline was 4.0 (2.7) (ranging from 0 to 11) corresponding to an urticaria uncontrolled population (UCT <12). Approximately half of the participants (115 [46.7%]) had angioedema at baseline (AAS7 score >0), with a mean (SD) AAS7 score of 37.2 (25.7) (ranging from 4 to 104). All participants were receiving H1-antihistamines for CSU at baseline, with 45.3% on standard dose, 34.3% on 2- to 3fold of standard dose, and 20.4% on 4-fold of standard dose.

Medical history and comorbid conditions associated with chronic spontaneous urticaria

Overall, the medical history and comorbid conditions associated with chronic spontaneous urticaria were balanced between the 2 intervention groups. The most common medical history relevant to CSU was angioedema reported in 57.7% of participants. Other common medical histories that were ongoing at baseline (in >10% of participants overall) were allergic rhinitis (24.0%) and asthma (17.1%). Of note, 8.5% of participants had ongoing food allergy. One participant had active AD at entry (as per exclusion criterion E04), and 5.7% of participants had previous history of AD. There were 19 participants with medical history of CSU associated autoimmune disorders such as autoimmune thyroid disease (autoimmune thyroiditis [10 [4.1%] participants] and Basedow's disease [6 [2.4%] participants]) and vitiligo (4 [1.6%] participants). Note that 1 participant presented both Basedow's disease and vitiligo.

Relevant prior and concomitant medications

Prior medications

The prior medications used for CSU, including H1-antihistamines and OCS, were balanced between intervention groups. All participants were receiving H1-antihistamines for CSU at baseline and 108 participants were previously exposed to omalizumab (4 were intolerant and 104 were incomplete responders).

The most frequently used prior medication for reasons other than CSU was levothyroxine sodium (23 [9.3%] participants). Of them, 11 participants had medical history of thyroid disease and prior use of levothyroxine.

Concomitant medications

During EFC16461 Study A, 5 participants (3 in the dupilumab group and 2 in the placebo group) received omalizumab, although prohibited by the protocol. All participants but one in placebo were administered omalizumab after study treatment schedule completion. In the dupilumab group, 1 participant received omalizumab 14 days after the last (Week 22) study intervention administration (on the same day as the EOT visit); the other 2 participants received omalizumab 35 days and 37 days, respectively, after their last (Week 22) study intervention administration during the follow-up period. In the placebo group, 1 participant received omalizumab 37 days after the last (Week 22) study intervention administration; the other participant received omalizumab 10 days after the Week 2 study intervention administration and prematurely discontinued study intervention after Week 2 due to lack of efficacy. None of the 5 participants experienced any concurrent AEs with the use of omalizumab. Oral corticosteroid use was allowed during the study as a rescue treatment. Sixteen (12.9%) participants in the dupilumab group and 18 (14.8%) participants in the placebo group received concomitant OCS.

Comparison across studies

Both studies had similar mean baseline disease characteristics.

Participants enrolled in EFC16461 Study B had an overall longer urticaria disease duration at baseline compared to EFC16461 Study A (9.1 years and 5.7 years, respectively). Although the studies enrolled similar proportions of participants with severe CSU disease activity (UAS7 ≥28 to ≤42; 69.4% in EFC16461 Study B and 70.3% in EFC16461 Study A, respectively), Study B had higher baseline AAS7 mean score (41.1 and 33.9) and higher baseline proportion of high dose H1antihistamine

use (63.6% and 47.8%). As per inclusion criteria, participants enrolled in EFC16461 Study A were naïve to omalizumab while participants enrolled in EFC16461 Study B were previously treated with omalizumab and the majority (104 [96.3%]) were incomplete responders to omalizumab. The participants enrolled in EFC16461 Study B were a more difficult to treat recalcitrant population, uncontrolled by approved therapies (including anti-IgE therapy), as compared to participants in EFC16461 Study A.

2.5.3. Adverse events

Overall treatment-emergent adverse events

The percentage of participants who reported at least 1 TEAE was similar between treatment groups (57.3% in the dupilumab group and 56.6% in the placebo group). Treatment-emergent AEs which were considered related to the study intervention by the Investigator occurred in 15 (12.1%) participants in the dupilumab group and 21 (17.2%) participants in the placebo group.

In the majority of participants, TEAEs were assessed as mild or moderate in severity. The severe TEAEs were reported in 3 (2.4%) participants in the dupilumab group and 5 (4.1%) participants in the placebo group. Treatment-emergent SAEs occurred in 12 participants (5 [4.0%] participants in the dupilumab group and 7 [5.7%] participants in the placebo group), including 1 TEAE leading to death in the placebo group (treatment-emergent SAE of completed suicide). No participants in the dupilumab group experienced TEAEs leading to death. Treatment-emergent AEs leading to permanent study intervention discontinuation as per the Investigator were reported in 2 (1.6%) participants in the dupilumab group (including 1 treatment-emergent SAE) and 4 (3.3%) participants in the placebo group.

Treatment-emergent AESIs were reported in 2 (1.6%) participants in the dupilumab group (medically confirmed systemic hypersensitivity reaction [urticaria] in 1 participant and pregnancy in another participant) and in 2 (1.6%) participants in the placebo group. TEAEs belonging to "Other selected AE groupings" category were reported in 16 (12.9%) participants in the dupilumab group and 15 (12.3%) in the placebo group. Most of these TEAEs were in the injection site reaction grouping (HLT) with similar incidences between the two intervention groups. Exposure-adjusted incidence rates of participants with at least 1 TEAE were higher in the placebo group compared to the dupilumab group (142.2 participants per 100 PY in the dupilumab group versus 165.5 participants per 100 PY in the placebo group, see Table 41).

Table 41. Number (%) of participants with TEAE(s) per 100 patient-years that occurred with a frequency >=2% in any treatment group by Primary SOC and PT – Pooled safety population

Primary System Organ Class Preferred Term nP/PY (nP/100 PY)	Placebo (N=122)	Dupilumab (N=124)
Any event	69/41.7 (165.5)	71/49.9 (142.2)
Infections and infestations	26/61.8 (42.0)	27/72.2 (37.4)
COVID-19	5/72.4 (6.9)	6/79.4 (7.6)
Pharyngitis	1/73.2 (1.4)	3/80.3 (3.7)
Nasopharyngitis	7/69.9 (10.0)	2/80.1 (2.5)
Urinary tract infection	3/71.8 (4.2)	1/80.4 (1.2)
Nervous system disorders	7/70.8 (9.9)	3/79.3 (3.8)
Headache	4/71.6 (5.6)	2/79.8 (2.5)
Vascular disorders	2/73.1 (2.7)	3/79.8 (3.8)
Hypertension	1/73.6 (1.4)	3/79.8 (3.8)
Skin and subcutaneous tissue disorders	24/63.4 (37.8)	21/71.8 (29.2)
Chronic spontaneous urticaria	9/69.5 (12.9)	10/76.8 (13.0)
Angioedema	5/71.2 (7.0)	3/79.4 (3.8)
Urticaria	2/72.7 (2.8)	3/79.6 (3.8)
Dermatitis contact	3/72.6 (4.1)	1/80.2 (1.2)

Primary System Organ Class Preferred Term nP/PY (nP/100 PY)	Placebo (N=122)	Dupilumab (N=124)
Dermatitis atopic	3/72.9 (4.1)	0/80.8
Musculoskeletal and connective tissue disorders	10/70.6 (14.2)	5/78.1 (6.4)
Back pain	3/72.3 (4.2)	0/80.8
General disorders and administration site conditions	17/65.5 (26.0)	13/74.1 (17.5)
Injection site reaction	3/72.2 (4.2)	5/78.1 (6.4)
Injection site erythema	7/70.4 (9.9)	3/79.1 (3.8)
Injection site pain	3/71.7 (4.2)	3/79.8 (3.8)
Investigations	7/70.8 (9.9)	4/79.0 (5.1)
Alanine aminotransferase increased	0/73.6	3/79.6 (3.8)
Blood creatine phosphokinase increased	3/72.2 (4.2)	0/80.8
Injury, poisoning and procedural complications	8/69.9 (11.4)	14/74.7 (18.8)
Accidental overdose	2/72.9 (2.7)	4/78.9 (5.1)

TEAE: Treatment-emergent adverse event, SOC: System organ class, PT: Preferred term

MedDRA 25.0

nP= number of participants with an event, PY=total patient-years in the treatment-emergent period, nP/100 PY = number of participants with at least one event per 100 patient-years.

Note: For participants with event, patient-years are calculated up to the date of the first incidence; for participants without event, patient-years correspond to the length of the treatment-emergent period.

Table sorted by SOC internationally agreed order and decreasing percentage of PT in Dupilumab group.

Only PTs with at least 2% in at least one group are presented.

PGM=PRODOPS/SAR231893/OVERALL/ISS_CSU_2021/REPORT/PGM/ae_socpt_py_s_t.sas
OUT=REPORT/OUTPUT/ae_socpt_py_freq2_s_t_i.rtf (24AUG2022 5:02)

Common Adverse Events

The number and percentage of participants with TEAE(s) that occurred with a frequency ≥2% in any intervention group by SOC and PT is provided in Table 42. The most frequently reported TEAEs at the SOC level (≥10% in any intervention group; number of participants [%] in the dupilumab group and number of participants [%] in the placebo group, respectively) were:

• Infections and infestations (27 [21.8%] and 26 [21.3%]),

• Skin and subcutaneous tissue disorders (21 [16.9%] and 24 [19.7%]),

• General disorders and administration site conditions (13 [10.5%] and 17 [13.9%]),

• Injury, poisoning, and procedural complications (14 [11.3%] and 8 [6.6%]).

The incidence of TEAEs in the 4 above-mentioned SOCs was similar between the dupilumab and placebo groups (no difference ≥5% between intervention group)

At the PT level, TEAEs that occurred with a frequency ≥2% in either study intervention group and were reported more frequently in the dupilumab group compared to the placebo group by at least 1% included:

• Injection site reaction (5 [4.0%] versus 3 [2.5%]),

• Accidental overdose (4 [3.2%] versus 2 [1.6%]),

• Pharyngitis (3 [2.4%] versus 1 [0.8%]),

• Hypertension (3 [2.4%] versus 1 [0.8%]),

• Alanine aminotransferase increased (3 [2.4%] versus 0).

For all these TEAEs, when comparing the dupilumab group to the placebo group, the lower bound of the 95% CI of risk difference was <0 and the lower bound of the 95% CI of hazard ratio was <1, therefore not demonstrating a significant difference between dupilumab and placebo (Table 42).

Treatment-emergent AEs that were reported with a frequency ≥2% in either study intervention group, less frequently in the dupilumab group compared to the placebo group with a difference of at least 1% included:

• Injection site erythema (3 [2.4%] versus 7 [5.7%]),

• Nasopharyngitis (2 [1.6%] versus 7 [5.7%]),

• Angioedema (3 [2.4%] versus 5 [4.1%]),

• Headache (2 [1.6%] versus 4 [3.3%]),

• Dermatitis contact (1 [0.8%] versus 3 [2.5%]),

• Urinary tract infection (1 [0.8%] versus 3 [2.5%]),

• Dermatitis atopic (0 versus 3 [2.5%]),

• Back pain (0 versus 3 [2.5%]),

• Blood creatine phosphokinase increased (0 versus 3 [2.5%]).

Table 42. Number (%) of participants with TEAE(s) that occurred with a frequency >=2% in any treatment group with risk differences and hazard ratios (95% CI) by Primary SOC and PT – Pooled safety population

Primary System Organ Class Preferred Term n (%)	Placebo (N=122)	Dupilumab (N=124)	Dupilumab vs Placebo	
			Risk difference (95% CI)[a]	Hazard ratio (95% CI)[b]
Any event	69 (56.6)	71 (57.3)	0.01 (-0.12 to 0.13)	0.92 (0.66 to 1.28)
Infections and infestations	26 (21.3)	27 (21.8)	0.00 (-0.10 to 0.11)	0.93 (0.54 to 1.59)
COVID-19	5 (4.1)	6 (4.8)	0.00 (-0.05 to 0.06)	1.13 (0.34 to 3.70)
Pharyngitis	1 (0.8)	3 (2.4)	0.02 (-0.03 to 0.07)	2.77 (0.29 to 26.69)

Primary System Organ Class Preferred Term n (%)	Placebo (N=122)	Dupilumab (N=124)	Risk difference (95% CI)[a]	Hazard ratio (95% CI)[b]
Nasopharyngitis	7 (5.7)	2 (1.6)	-0.05 (-0.10 to 0.01)	0.27 (0.06 to 1.28)
Urinary tract infection	3 (2.5)	1 (0.8)	-0.02 (-0.07 to 0.03)	0.32 (0.03 to 3.12)
Nervous system disorders	7 (5.7)	3 (2.4)	-0.03 (-0.09 to 0.03)	0.39 (0.10 to 1.52)
Headache	4 (3.3)	2 (1.6)	-0.02 (-0.08 to 0.03)	0.47 (0.09 to 2.59)
Vascular disorders	2 (1.6)	3 (2.4)	0.00 (-0.04 to 0.05)	1.49 (0.25 to 8.94)
Hypertension	1 (0.8)	3 (2.4)	0.01 (-0.04 to 0.06)	3.00 (0.31 to 28.85)
Skin and subcutaneous tissue disorders	24 (19.7)	21 (16.9)	-0.02 (-0.12 to 0.08)	0.80 (0.44 to 1.44)
Chronic spontaneous urticaria	9 (7.4)	10 (8.1)	-0.00 (-0.07 to 0.07)	1.06 (0.43 to 2.61)
Angioedema	5 (4.1)	3 (2.4)	-0.01 (-0.07 to 0.05)	0.56 (0.13 to 2.33)
Urticaria	2 (1.6)	3 (2.4)	0.00 (-0.05 to 0.06)	1.39 (0.23 to 8.35)
Dermatitis contact	3 (2.5)	1 (0.8)	-0.02 (-0.07 to 0.03)	0.29 (0.03 to 2.82)
Dermatitis atopic	3 (2.5)	0	-0.03 (-0.08 to 0.01)	0.00 (0.00 to NC)
Musculoskeletal and connective tissue disorders	10 (8.2)	5 (4.0)	-0.05 (-0.12 to 0.02)	0.47 (0.16 to 1.37)
Back pain	3 (2.5)	0	-0.03 (-0.08 to 0.02)	0.00 (0.00 to NC)
General disorders and administration site conditions	17 (13.9)	13 (10.5)	-0.04 (-0.12 to 0.05)	0.73 (0.36 to 1.51)
Injection site reaction	3 (2.5)	5 (4.0)	0.02 (-0.04 to 0.07)	1.64 (0.39 to 6.86)
Injection site erythema	7 (5.7)	3 (2.4)	-0.05 (-0.10 to 0.01)	0.41 (0.11 to 1.60)
Injection site pain	3 (2.5)	3 (2.4)	0.00 (-0.05 to 0.06)	0.97 (0.20 to 4.81)
Investigations	7 (5.7)	4 (3.2)	-0.03 (-0.09 to 0.03)	0.52 (0.15 to 1.79)
Alanine aminotransferase increased	0	3 (2.4)	0.03 (-0.02 to 0.08)	26785633.79 (0.00 to NC)
Blood creatine phosphokinase increased	3 (2.5)	0	-0.03 (-0.08 to 0.02)	0.00 (0.00 to NC)
Injury, poisoning and procedural complications	8 (6.6)	14 (11.3)	0.05 (-0.03 to 0.13)	1.67 (0.70 to 3.98)
Accidental overdose	2 (1.6)	4 (3.2)	0.02 (-0.03 to 0.07)	2.01 (0.37 to 10.96)

TEAE: Treatment-emergent adverse event, SOC: System organ class, PT: Preferred term

MedDRA 25.0

a 95% confidence interval calculated using Miettinen and Nurminen method stratified by study.

b Calculated from Cox proportional hazards model with intervention in the model and stratified by study. Participants without an event were censored at end of treatment-emergent period.

n (%) = number and percentage of participants with at least one AE during the treatment-emergent period.

Table sorted by SOC internationally agreed order and decreasing percentage of PT in Dupilumab group.

Only PTs with at least 2% in at least one group are presented.

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Comparison across chronic spontaneous urticaria studies

The overall incidence of TEAEs was comparable between EFC16461 Study B and Study A, including a low incidence of treatment-emergent SAEs in both studies. Reported TEAEs were comparable between participants that were previously treated with omalizumab (EFC16461 Study B) or naïve to omalizumab (EFC16461 Study A) with the exception of Skin and subcutaneous tissue disorders SOC:

• in EFC16461 Study B, a higher incidence of participants with any TEAE (difference ≥5%) was observed in the dupilumab group compared to the placebo group (11 [20.4%] and 6 [11.1%],

respectively), mainly driven by an imbalance in the PT chronic spontaneous urticaria (7 [13.0%] and 3 [5.6%]). CSU-related TEAEs (in the HLGT of angioedema and urticaria) were reported in 14 (13.0%) participants overall (10 [18.5%] in the dupilumab group versus 4 [7.4%] in the placebo group) including the PTs of chronic spontaneous urticaria (7 [13.0%], 3 [5.6%]), angioedema (2 [3.7%], 0 [0.0%]), idiopathic angioedema

(1 [1.9%], 0 [0.0%]), and urticaria (0 [0.0%], 1 [1.9%]). All these events were of mild or moderate intensity and resolved with corrective treatment or rescue therapy mainly including H1-antihistamines and corticosteroids; none of the events were assessed as related to the study intervention as per Investigator and none led to IMP discontinuation. There were 2 participants with treatment-emergent SAEs potentially associated with CSU, both in the dupilumab group (chronic spontaneous urticaria and idiopathic angioedema). The majority (6 out of 10) of the participants with TEAEs potentially associated with CSU in the dupilumab group occurred early on in the study intervention period and by Week 24

the majority of these 10 participants had decreases in itch (ISS7) and hives (HSS7). The baseline disease severity for all the 10 participants in the dupilumab group was 'severe' as defined by a UAS7 ≥28. In the placebo group, the baseline disease severity was ‘severe’ for 2 of the 4 participants.

• in EFC16461 Study A, a lower incidence of participants with any TEAE (difference ≥5%) was observed in the dupilumab group compared to the placebo group (10 [14.3%] and 18 [26.5%], respectively), mainly driven by PTs of chronic spontaneous urticaria (3 [4.3%] and 6 [8.8%]) and angioedema (1 [1.4%] and 5 [7.4%]). CSU-related TEAEs (in the HLGT of angioedema and urticaria) were reported in 19 (13.8%) participants overall (6 [8.6%] in the dupilumab group and 13 [19.1%] in the placebo group). This was consistent with the clinical presentation in patients with uncontrolled CSU, some of the TEAEs observed more frequently in the placebo group were related to CSU flares.

Adverse events in adolescents and children

There were 6 adolescents (aged 12 to <18 years) included in the safety pool (3 in each study intervention group). None of the adolescents in the dupilumab group experienced any TEAE. Two out of 3 adolescents in the placebo group experienced a TEAE (asymptomatic COVID-19 in 1 participant and mild post procedural fever due to “covid vaccine injection” in 1 participant). There were no TEAEs reported in the 2 children (aged 6 to <12 years), both enrolled in the dupilumab group in EFC16461 Study A and who discontinued study intervention early.

Treatment-emergent adverse events by Investigator causality

Treatment-emergent AEs considered to be related to the study intervention (as per Investigator) were reported less frequently in the dupilumab group (15 [12.1%]) than in the placebo group (21 [17.2%]). Most of the study intervention-related TEAEs (number of participants [%] in the dupilumab group and number of participants [%] in the placebo group, respectively) were under the injection site reactions HLT (9 [7.3%] and 12 [9.8%]): PTs of injection site erythema (3 [2.4%] and 6 [4.9%]), injection site reaction (4 [3.2%] and 3 [2.5%]), injection site pain (2 [1.6%] and 3 [2.5%]), injection site induration (2 [1.6%] and 0), and injection site pruritus (0 and 1 [0.8%]) (see Table 43).

Table 43. Number (%) of participants with TEAE(s) related to IMP as per Investigator's judgement by Primary SOC and PT – Pooled safety population

Primary System Organ Class Preferred Term n (%)	Placebo (N=122)	Dupilumab (N=124)
Any event	21 (17.2)	15 (12.1)
Infections and infestations	3 (2.5)	1 (0.8)
Oral herpes	2 (1.6)	1 (0.8)
Conjunctivitis	1 (0.8)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.8)	0
Skin papilloma	1 (0.8)	0
Nervous system disorders	2 (1.6)	0
Headache	1 (0.8)	0
Migraine	1 (0.8)	0
Somnolence	1 (0.8)	0
Eye disorders	0	1 (0.8)
Conjunctivitis allergic	0	1 (0.8)
Ear and labyrinth disorders	1 (0.8)	1 (0.8)
Vertigo	0	1 (0.8)
Vertigo positional	1 (0.8)	0
Gastrointestinal disorders	1 (0.8)	0
Aphthous ulcer	1 (0.8)	0
Skin and subcutaneous tissue disorders	3 (2.5)	2 (1.6)
Chronic spontaneous urticaria	1 (0.8)	1 (0.8)
Urticaria	1 (0.8)	1 (0.8)
Eczema asteatotic	1 (0.8)	0
Musculoskeletal and connective tissue disorders	1 (0.8)	0
Arthritis	1 (0.8)	0
General disorders and administration site conditions	12 (9.8)	11 (8.9)
Injection site reaction	3 (2.5)	4 (3.2)
Injection site erythema	6 (4.9)	3 (2.4)
Injection site induration	0	2 (1.6)
Injection site pain	3 (2.5)	2 (1.6)
Asthenia	0	1 (0.8)
Fatigue	0	1 (0.8)
Injection site pruritus	1 (0.8)	0

Severity of treatment-emergent adverse events

The majority of TEAEs were of mild or moderate intensity with similar incidences in both study intervention groups. TEAEs considered as severe were reported in 3 (2.4%) participants in the dupilumab group (depression, angioedema, and intestinal obstruction) and 5 (4.1%) participants in the placebo group (depression and completed suicide in 1 participant, dyspnea, abdominal pain upper and nausea in 1 participant, angioedema in 1 participant, dermatitis atopic in 1 participant, and blood creatine phosphokinase increased in 1 participant).

2.5.4. Serious adverse event/deaths/other significant events

No participants had TEAE leading to death in the dupilumab group. There was 1 participant with TEAE leading to death in the placebo group (completed suicide on Day 48). The medical history included alcoholism and ongoing depression over the past 3 years.

Treatment-emergent SAEs were reported in 5 (4.0%) participants in the dupilumab group and 7 (5.7%) participants in the placebo group (1 participant had 3 SAEs) (Table 44). Each individual treatment-emergent SAE PT was reported only once in either of the intervention groups. All treatment-emergent SAEs were assessed as not related to the study intervention by the Investigator. All events in the dupilumab group resolved or were resolving.

More detailed information on the SAEs included in the study reports are provided below.

Table 44. Number(%) of participants with treatment-emergent SAE(s) by Primary SOC and PT – Pooled safety population

Primary System Organ Class Preferred Term n (%)	Placebo (N=122)	Dupilumab (N=124)
Any event	7 (5.7)	5 (4.0)
Infections and infestations	1 (0.8)	0
COVID-19 pneumonia	1 (0.8)	0

Primary System Organ Class Preferred Term n (%)	Placebo (N=122)	Dupilumab (N=124)
Psychiatric disorders	1 (0.8)	1 (0.8)
Depression	0	1 (0.8)
Completed suicide	1 (0.8)	0
Respiratory, thoracic and mediastinal disorders	1 (0.8)	0
Dyspnoea	1 (0.8)	0
Gastrointestinal disorders	1 (0.8)	2 (1.6)
Haemorrhoids	0	1 (0.8)
Intestinal obstruction	0	1 (0.8)
Abdominal pain upper	1 (0.8)	0
Nausea	1 (0.8)	0
Skin and subcutaneous tissue disorders	2 (1.6)	2 (1.6)
Chronic spontaneous urticaria	0	1 (0.8)
Idiopathic angioedema	0	1 (0.8)
Angioedema	1 (0.8)	0
Dermatitis atopic	1 (0.8)	0
Musculoskeletal and connective tissue disorders	2 (1.6)	0
Osteoarthritis	1 (0.8)	0
Pain in extremity	1 (0.8)	0

SAE: Serious adverse event, SOC: System organ class, PT: Preferred term
MedDRA 25.0
n (%) = number and percentage of participants with at least one SAE during the treatment-emergent period.
Table sorted by SOC internationally agreed order and decreasing percentage of PT in Dupilumab group.
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The participants with treatment-emergent SAEs were:

Part B

In the dupilumab group:

• One participant had an SAE of moderate chronic spontaneous urticaria ("generalized chronic spontaneous urticaria exacerbation") on Day 30 (14 days after the Week 2 IMP administration) for which the participant was hospitalized for 3 days. The participant recovered from the event. The IMP was permanently discontinued after Week 2 for lack of efficacy. The participant had a treatment-emergent ADA response with low titer (60 nmol/L) on Day 29, which had no direct association with the SAE.

• One participant with a long history of chronic constipation and intestinal obstruction and abdominal surgery 53 years ago had an SAE of severe intestinal obstruction on Day 252 (3 months after Week 22 and the last IMP administration) for which the participant was hospitalized for 9 days. At the time of this report, the participant was recovering from the event.

• One participant with a medical history of angioedema had an SAE of moderate idiopathic angioedema (worsened from mild to moderate) on Day 113 (the same day as Week 16 IMP administration), for which the participant was hospitalized for 7 days. The participant recovered from the event.

In the placebo group:

• One participant with a medical history of arthrosis of left foot underwent a medical procedure of arthrolysis of the left foot in the hospital on Day 34 (5 days after the Week 4 IMP administration) and was discharged home the next day. The event was reported as an SAE of osteoarthritis of moderate intensity. The participant recovered from the event without sequelae.

• One participant with a medical history of pain in extremity had an SAE of moderate pain in extremity ("worsening pain in extremity of unknown origin") on Day 91 (13 days after the Week 10 IMP administration), for which the participant was hospitalized for investigation and

treatment. The event had not resolved at the time of this report. The participant withdrew from study intervention after Week 10 (Withdrawal by subject - lack of efficacy).

Part A

In the dupilumab group:

• One participant with medical history of depression was hospitalized with an SAE of severe depression on Study Day 114 (1 day after the last [Week 16] IMP injection). The participant also had a non-serious TEAE of moderate borderline personality disorder on the same day. Both events led to permanent IMP discontinuation after Week 16. The participant recovered from the event of depression, but not from borderline personality disorder.

• Participant No. 016461-156-0008-40003 with medical history of hemorrhoids had new complaint of hemorrhoids starting from Day 20 (5 days after the Week 2 IMP injection). The participant was late hospitalized (on Day 92), underwent surgery, and recovered from the event.

In the placebo group:

• One participant (death, completed suicide).

• One participant with medical history of eczema had an SAE of severe dermatitis atopic on Day 42 (10 days after the last [Week 4] dose of IMP) that led to hospitalization. The participant recovered from the event.

• One participant with no medical history of angioedema had an SAE of severe angioedema on Day 17 (2 days after the Week 2 IMP injection) that led to hospitalization. The participant recovered from the event.

• One participant had a TEAE of COVID-19 pneumonia on Day 33 (4 days after the last [Week 4] dose of IMP) which became serious and led to hospitalization on Day 37. The participant received corrective treatments that included levilimab (a protocol prohibited concomitant medication) and the IMP was subsequently discontinued per protocol. The participant recovered from the event. The participant also had a post-treatment SAE of appendicitis on Day 181 that led to hospitalization (not related to the IMP, recovered).

• One participant with medical history of Type-2 diabetes and obesity had 3 SAEs of severe dyspnea, abdominal pain upper, and nausea, all of unknown origin, on Day 251 (96 days after the last [Week 22] dose of IMP) that led to hospitalization. The participant recovered from the events. No further information was available regarding the origin and final diagnosis for these events.

2.5.5. Adverse Events of Special Interest

An overview of the number (%) of participants with treatment-emergent AESIs or other selected AE groupings events by category is provided in Table 45.

Treatment-emergent AESIs were reported in 2 (1.6%) participants in each treatment group. The most frequently reported treatment-emergent "other selected AE groupings" was injection site reaction HLT (11 [8.9%] participants in the dupilumab group and 13 [10.7%] participants in the placebo group).

Potential drug-related hepatic disorder grouping retrieved 6 nonserious TEAEs in 4 (3.2%) participants (all in the dupilumab group). Conjunctivitis groupings (narrow, broad and FDA criteria) each identified the same 2 (1.6%) participants in the dupilumab group and 2 (1.6%) in the placebo group. Severe or serious infection groupings was reported in 1 (0.8%) participant in the placebo group (serious COVID-19 pneumonia).

The following treatment-emergent AESIs or other selected AE groupings were not reported in either intervention group: anaphylactic reactions, helminthic infections, severe type of conjunctivitis or blepharitis, keratitis, clinically symptomatic eosinophilia, significant ALT elevation, symptomatic overdose with IMP or NIMP, serious injection site reaction or severe injection site reaction that lasted longer than 24 hours, and malignancy.

Selected treatment-emergent AESIs are described in more detail below.

Table 45. Number (%) of participants with treatment-emergent AESIs and other selected AE grouping events by category – Pooled safety population

AE Category n (%)	Placebo (N=122)	Dupilumab (N=124)
Any treatment emergent AESI	2 (1.6)	2 (1.6)
Anaphylactic reactions (medically reviewed)	0	0
Systemic hypersensitivity reactions (medically reviewed)	1 (0.8)	1 (0.8)
Helminthic infections	0	0
Any severe type of conjunctivitis	0	0
Any severe type of blepharitis	0	0
Keratitis	0	0
Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)	0	0
Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP/NIMP	1 (0.8)	1 (0.8)
Significant ALT elevation	0	0
Symptomatic overdose with IMP	0	0
Symptomatic overdose with NIMP	0	0
Other selected AEs	15 (12.3)	16 (12.9)
Serious injection site reactions or severe injection site reactions that last longer than 24 hours	0	0
Severe or serious infection	1 (0.8)	0
Drug-related hepatic disorder	0	4 (3.2)
Injection site reaction	13 (10.7)	11 (8.9)
Malignancy	0	0
Conjunctivitis (narrow)	2 (1.6)	2 (1.6)
Conjunctivitis (broad)	2 (1.6)	2 (1.6)
Conjunctivitis (FDA)[a]	2 (1.6)	2 (1.6)
Keratitis (FDA) [a]	0	0

AESI: Adverse event of special interest, IMP: Investigational medicinal product, NIMP: Non investigational medicinal product
MedDRA 25.0

a Labeling subgroup of preferred terms included in the USPI for Dupixent.

n (%) = number and percentage of participants with at least one AESI/other AE grouping event during the treatment-emergent period.

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Anaphylactic Reactions and Systemic hypersensitivity reactions (medically reviewed) (AESI)

Hypersensitivity events confirmed as being systemic after Sponsor's medical review were reported in 2 participants, 1 [0.8%] in the dupilumab group (a short summary is provided below) and 1 [0.8%] in the placebo group (nonserious moderate urticaria ["generalized urticaria exacerbation 48h post Vazevria® vaccine [COVID-19]"]). One participant (EFC16461 Study A) in the dupilumab group experienced a nonserious TEAE of moderate urticaria ("hives and itching all over the body in reaction to COVID-19 vaccine") one day after receiving the first dose of COVID-19 vaccine tozinameran/Comirnaty®) and the study intervention. The event resolved with corrective treatment (prednisone) after 10 days and was assessed as not related to the IMP by the Investigator.

Conjunctivitis (narrow, broad, FDA; other selected AE groupings)

Conjunctivitis groupings (based on CMQ broad criteria, CMQ narrow criteria, and FDA criteria) each identified the same 4 TEAEs of non-severe conjunctivitis (2 [1.6%] in the dupilumab group and 2 [1.6%] in the placebo group) (see Table 45). A summary of the non-severe conjunctivitis reported in 2 participants in the dupilumab group (both in EFC16461 Study B) is provided below:

• One participant with no medical history of conjunctivitis experienced a nonserious TEAE of mild conjunctivitis allergic on Day 15 (the same day of the Week 2 study intervention administration). The

event was assessed as related to the study intervention by the Investigator, but study intervention was continued without interruption or corrective treatment. At the time of this report, the event had not resolved.

• One participant with no medical history of conjunctivitis experienced a nonserious TEAE of mild conjunctivitis on Day 155 (the same day of the Week 22 study intervention administration). The event was assessed as not related to the study intervention by the Investigator, and the study intervention was continued without interruption. Conjunctivitis resolved after treatment with sulfacyl sodium 10 % eye drops.

Pregnancy (AESI)

Summary of the pregnancy that occurred in 1 female participant who became pregnant during the study intervention period in the dupilumab group is provided below:

• One participant (EFC16461 Study A) became pregnant on Day 42 (13 days after the Week 4 study intervention injection). As per the protocol, the study intervention was permanently discontinued, with the last dose of study intervention administered on Day 68 (Week 10). No AEs were reported during the pregnancy. The pregnancy was completed with delivery without complication on Day 324. No further information was available regarding the newborn's condition.

• Another pregnancy occurred in 1 participant in EFC16461 Study B in the placebo group during the follow-up period.

Significant ALT elevation (AESI) and potential drug-related hepatic disorders

No events of significant ALT elevation (AESI), defined as ALT >5×ULN if baseline ALT ≤2×ULN; or ALT >8×ULN if baseline ALT >2×ULN, were reported. Treatment-emergent events of potential drug-related hepatic disorder (other selected AE groupings) were reported in 4 participants, all (3.2%) in the dupilumab group, all were non-serious and did not lead to permanent study intervention discontinuation.

One participant had an event assessed as related to the study intervention by the Investigator (one participant [PT: alanine aminotransferase increased].

The events in the other participants were assessed as not related to the study intervention by the Investigator:

• One participant (EFC16461 Study B; age group: 40-49 years) with a medical history of obesity had a nonserious TEAE of mild hepatic steatosis along with a mild cholelithiasis during the off-treatment follow-up period on Day 232 (more than 2◦months after the Week 22 and the last study intervention administration). At the time of this report, the event had not resolved but stabilized.

• One participant (PT: alanine aminotransferase increased and hepatic steatosis; a short summary is provided in Section 3.1.1, alanine aminotransferase increased).

• One participant (PT: alanine aminotransferase increased and aspartate aminotransferase increased; a short summary is provided in Section 3.1.1, alanine aminotransferase increased.

No participants had PCSAs in liver function that met Hy's law criteria.

Injection site reaction (serious or severe injection site reaction that lasted longer than 24 hours)

No serious or severe injection site reaction that lasted longer than 24 hours were reported in either intervention group (Table 45).

Injection site reactions HLT TEAEs (including PTs of injection site erythema, injection site reaction, injection site pain, injection site induration, and injection site pruritus) were reported with similar incidences between the 2 intervention groups (36 events in 11 [8.9%] participants in the dupilumab group and 40 events in 13 [10.7%] participants in the placebo group) (Table 46). The 3 most common injection site reactions by PT were injection site erythema (3 [2.4%] participants in the dupilumab group and 7 [5.7%] participants in the placebo group), injection site reaction (5 [4.0%] and 3 [2.5%]), and injection site pain (3 [2.4%] and 3 [2.5%]). In most participants (9 out of 11 in the dupilumab group and 12 out of 13 in the placebo group) the events were assessed as related to the study intervention by the Investigator. All the events of injection site reactions (36 in the dupilumab group and 40 in the placebo group) were nonserious, mild or moderate (in the dupilumab group, 36 events were mild and in the placebo group 38 events were mild and 2 were moderate). All resolved without corrective treatment and without permanent intervention discontinuation.

Table 46. Summary of participants with injection site reactions high level term – Pooled safety population

Injection site reactions	Placebo (N=122)	Dupilumab (N=124)
Participants with any TEAE	13 (10.7)	11 (8.9)
Participants with any SAE	0	0
Participants with any treatment-emergent SAE	0	0
Participants with any AE leading to death	0	0
Participants with any TEAE leading to death	0	0
Participants with any TEAE leading to permanent study intervention discontinuation	0	0
Participants with any TEAE related to IMP reported by investigator	12 (9.8)	9 (7.3)
Number of participants with any TEAE per 100 Patient-years	19.37	14.58
Maximal intensity		
Moderate	2 (1.6)	0
Severe	0	0
Corrective treatment		
Yes	0	0
Outcome		
Fatal	0	0
Not recovered/Not resolved	0	0
Recovered	13 (10.7)	11 (8.9)
Recovered with sequelae	0	0
Recovering	0	0
Unknown	0	0
Time to onset of first TEAE (days)		
Number	13	11
Mean (SD)	33.8 (37.2)	28.9 (29.8)
Median	17.0	15.0
Q1 ; Q3	2.0 ; 57.0	1.0 ; 43.0
Min ; Max	1 ; 127	1 ; 84
Kaplan-Meier estimates for probability of a participant with ≥1 TEAE (95% CI) up to		
12 weeks	0.100 (0.054 to 0.161)	0.089 (0.047 to 0.148)
24 weeks	0.109 (0.061 to 0.172)	0.089 (0.047 to 0.148)
Average duration of TEAEs (days)[a]		
Number	13	11
Mean (SD)	0.8 (1.7)	1.8 (2.3)
Median	0.1	1.0
Q1 ; Q3	0.0 ; 1.0	0.1 ; 2.0
Min ; Max	0 ; 6	0 ; 7

Injection site reactions	Placebo (N=122)	Dupilumab (N=124)
Average duration of TEAEs [n(%)][a]		
>0 to ≤2 days	12 (9.8)	9 (7.3)
>2 to ≤7 days	1 (0.8)	2 (1.6)
>7 days to ≤1 month	0	0
>1 to ≤3 months	0	0
>3 to ≤6 months	0	0
>6 months	0	0
Cumulative duration of TEAEs (days)[b]		
Number	13	11
Mean (SD)	4.5 (14.0)	3.5 (3.6)
Median	0.3	2.0
Q1 ; Q3	0.0 ; 2.0	1.0 ; 7.0
Min ; Max	0 ; 51	0 ; 11
Number of participants who have ISR associated with / Number of participants who have		
Week 0 injection	4/122 (3.3)	4/124 (3.2)
Week 2 injection	3/121 (2.5)	4/120 (3.3)
Week 4 injection	5/119 (4.2)	4/122 (3.3)
Week 6 injection	2/111 (1.8)	4/119 (3.4)
Week 8 injection	4/109 (3.7)	2/119 (1.7)
Week 10 injection	4/105 (3.8)	4/118 (3.4)
Week 12 injection	4/100 (4.0)	3/113 (2.7)
Week 14 injection	2/96 (2.1)	2/114 (1.8)
Week 16 injection	2/96 (2.1)	2/113 (1.8)
Week 18 injection	4/95 (4.2)	2/113 (1.8)
Week 20 injection	2/94 (2.1)	1/112 (0.9)
Week 22 injection	2/92 (2.2)	1/112 (0.9)
Participants with		
1 episode of ISR	4/13 (30.8)	5/11 (45.5)
2 episodes of ISRs	6/13 (46.2)	1/11 (9.1)
≥3 episodes of ISRs	3/13 (23.1)	5/11 (45.5)
Number of ISRs with duration		
<24 hours	25/40 (62.5)	17/36 (47.2)
≥24-<72 hours	10/40 (25.0)	16/36 (44.4)
≥72 hours	5/40 (12.5)	3/36 (8.3)

TEAE: Treatment-emergent adverse event, SAE: Serious adverse event, NIMP: Non Investigational Medicinal Product, ISR: Injection site reaction, HLT: High level term

MedDRA 25.0

a Average duration is the average over all occurrences that resolved.

b Cumulative duration is the total duration of the event over time.

Injection site reactions are identified as AE with HLT as injection site reactions.

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Table 47. Number (%) of participants with injection site reactions by PT during the treatment-emergent period – Pooled safety population

Preferred Term n (%)	Placebo (N=122)	Dupilumab (N=124)
Any Class	13 (10.7)	11 (8.9)
Injection site reaction	3 (2.5)	5 (4.0)
Injection site erythema	7 (5.7)	3 (2.4)
Injection site pain	3 (2.5)	3 (2.4)
Injection site induration	0	2 (1.6)
Injection site pruritus	1 (0.8)	0

PT: Preferred term, HLT: High level term
MedDRA 25.0
Injection site reactions are identified as AE with HLT as injection site reactions.
PGM=PRODOPS/SAR231893/OVERALL/ISS_CSU_2021/REPORT/PGM/ae_isrpt_s_t.sas OUT=REPORT/OUTPUT/ae_isrpt_s_t_i.rtf (24AUG2022 4:55)

2.5.6. Adverse Drug Reactions

The primary assessment for ADRs was conducted on the pooled safety population (N=246 participants).

Identification of ADRs was based on the following criteria:

• Quantitative Criteria: The PTs with incidence ≥2% in the dupilumab group and difference ≥1% versus placebo group and with lower bound of the 95% CI of relative risk >1 compared to placebo.

• Qualitative Criteria: The PTs with incidence ≥2% in the dupilumab group and difference ≥1% versus placebo group were identified and reviewed for potential causal relationship taking into consideration biologic plausibility, presence of potential confounders and/or alternative explanation, and plausible exposure relationship.

• In addition, previously established ADRs for approved indications (AD, asthma, CRSwNP, EoE, and PN) with incidence ≥2% in the dupilumab and greater than placebo group were also reviewed for potential causal relationship with dupilumab.

Quantitative criteria

No events met the quantitative criteria described above.

Qualitative criteria

The following PTs with an incidence ≥2% in the dupilumab group and difference ≥1% versus placebo group (although the quantitative criteria was not met) was considered as an ADR (ie, lower bound of the 95% CI of relative risk ≤1 compared to placebo) (Figure 36):

• Injection site reaction was reported in 5 (4.0%) participants in the dupilumab group and 3 (2.5%) participants in the placebo group.

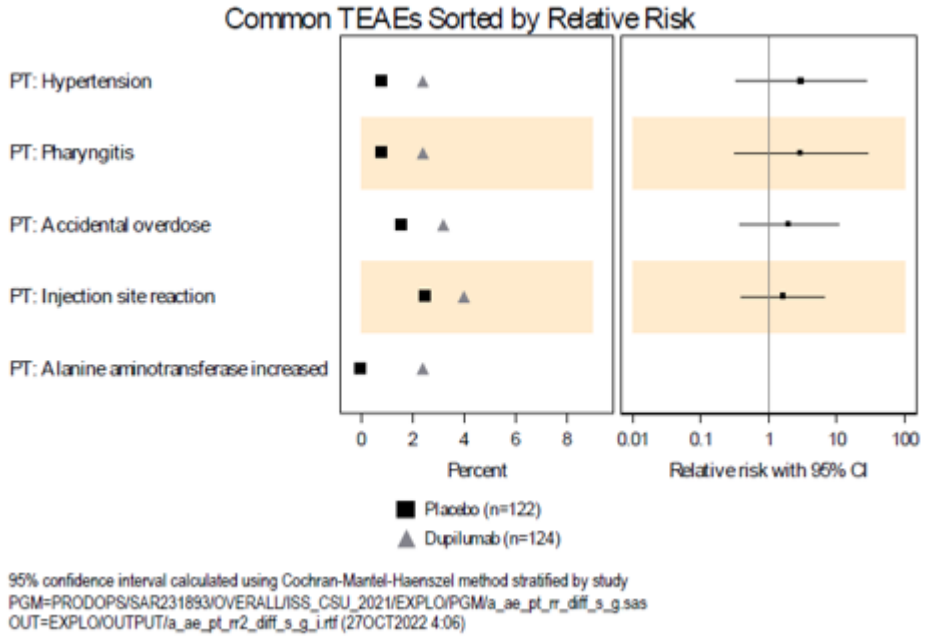
Previously established ADRs for approved indications (AD, asthma, CRSwNP, EoE, and PN)

The review of previously established ADRs for approved indications (AD, asthma, CRSwNP, EoE and PN), with an incidence ≥2% in the dupilumab group and greater than placebo group did not find additional PTs (other than the PT of injection site reaction) that were assessed as ADRs. The frequency of all other preferred terms in the dupilumab group was less than 2% and/or less than or equal to that in the placebo group.

In summary, the ADR identified in participants with CSU is the PT of injection site reaction (5 [4.0%] participants in the dupilumab group versus 3 [2.5%] participants in the placebo group) based on the

observed imbalance between study intervention groups and because injection site reactions are considered as ADRs in other approved indications for dupilumab. Overall, the incidence of injection site reaction in the dupilumab group was similar or lower than that observed in approved indications. No new ADRs were identified in the CSU population.

Figure 36. Forest plot of relative risk (95% CI) of TEAE(s) with PT ≥2% in dupilumab group and difference ≥1% versus placebo group – Pooled safety population



2.5.7. Laboratory findings

Clinical laboratory data

Clinical laboratory data were evaluated in the pooled safety population.

HEMATOLOGY

No clinically meaningful changes over time were observed in mean values of RBC, platelets, or WBC throughout the treatment-emergent period in the dupilumab and placebo group.

Blood eosinophil count

The mean blood eosinophil count at baseline was similar between intervention groups (0.164 Giga/L [SD 0.143] in the dupilumab group and 0.172 Giga/L [0.144] in the placebo group) and below the adult ULN (0.8 Giga/L). The maximal value observed at baseline was 0.78 Giga/L in the dupilumab group and 0.78 Giga/L in the placebo group.

At week 24, a slight increase in mean (SD) blood eosinophil count change from baseline was observed in the dupilumab group (+0.032 Giga/L [0.243]) which returned to baseline value at Week 36 and that was driven by a few outliers. Although not clinically significant, this slight increase was observed in EFC16461 Study B but not in EFC16461 Study A (see Figures CSR Study B and A, 16.2.8.2.12).

CSR_B4-EFC16461-16.2.8-EN

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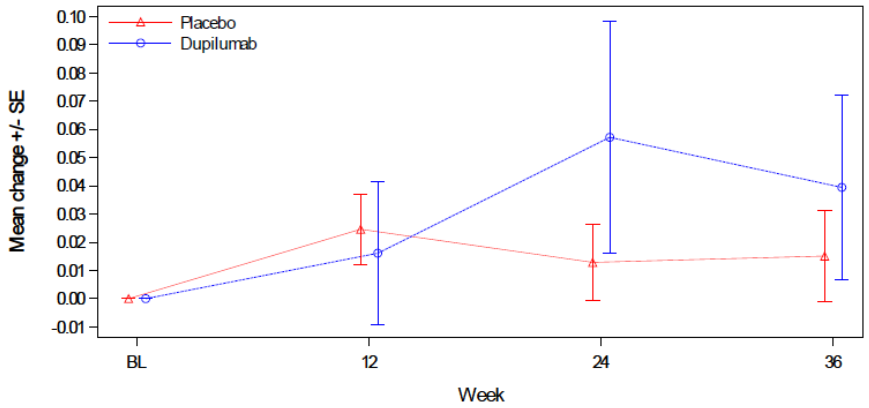
16.2.8 Clinical laboratory data
16.2.8.2 Descriptive tables and graphs
16.2.8.2.12 Eosinophils (10^9/L): Mean change (+/- SE) from baseline - Safety population



participants

Placebo	54	52	40	42
Dupilumab	53	49	43	46

Only on-treatment values are included, except for the Week 36 visit
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90/335

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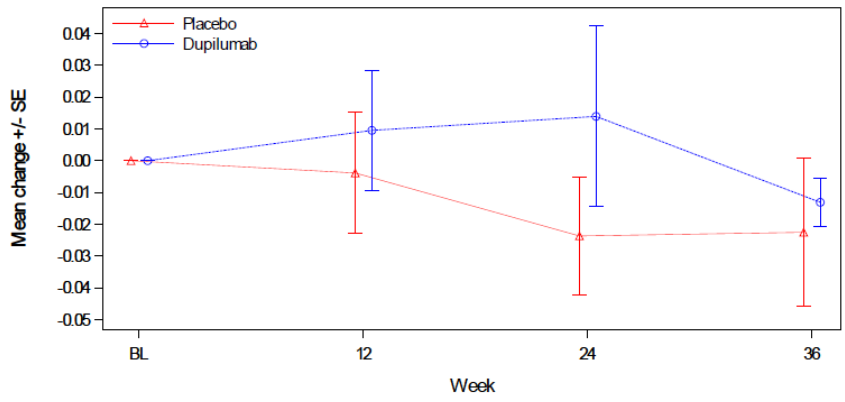
16.2.8 Clinical laboratory data
16.2.8.2 Descriptive tables and graphs
16.2.8.2.12 Eosinophils (10^9/L): Mean change (+/- SE) from baseline - Safety population



#participants

Placebo	67	57	46	53
Dupilumab	70	67	62	58

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92/351

Potentially clinically significant abnormality (PCSA)

The overall number of participants with PCSAs for hematology parameters during the TEAE period according to the baseline status was low and without clinically meaningful difference across the intervention groups. Among the participants with baseline values in the normal range or missing value,

the percentage of participants with PCSA in hematology parameters was similar between intervention groups. There were no PCSAs for hematocrit, platelets, nor lymphocytes and no other clinically meaningful trends observed. One adolescent participant in the dupilumab group had a postbaseline PCSA for high neutrophils.

Blood eosinophil PCSAs

For eosinophils (normal range in blood: 0.0 – 0.8 Giga/L), the incidence of post-baseline PCSA for high eosinophil count was 5 (4.1%) in the dupilumab group and 2 (1.7%) in the placebo group. Of the 7 participants with post-baseline PCSA, there was peak value >0.8 but <1.1 Giga/L in 3 participants (2 in the placebo group and 1 in the dupilumab group) and peak values at 1.33 Giga/L at Week 24 (baseline value at 0.74 Giga/L), 1.55 Giga/L at Week 36 (baseline value at 0.78 Giga/L), 1.60 Giga/L at Week 24 (baseline value at 0.03 Giga/L; screening value at 3.16 Giga/L), and 1.71 at Week 24 Giga/L (baseline value at 0.05 Giga/L), in the remaining participants in the dupilumab group. None of these participants experienced clinical symptoms associated with eosinophilia. The participant with peak eosinophil count of 1.71 Giga/L at Week 24 experienced a TEAE of contusion with skin bruise 2 days prior. For the other 6 participants, no concurrent AEs were reported. None of the participants had blood eosinophil counts ≥5 Giga/L; 9 (7.6%) in the dupilumab group and 9 (7.6%) in the placebo group had eosinophil count >0.5 Giga/L.

Individual clinically relevant abnormalities

No participants experienced hematological abnormalities that were considered treatment-emergent SAE or TEAE leading to a permanent study intervention discontinuation. Eosinophilia was not considered as a TEAE in any participant in either study intervention group, and in all cases was a self-limiting laboratory finding without any associated symptoms.

CLINICAL CHEMISTRY

Metabolic parameters

No clinically meaningful changes over time were observed in mean metabolic parameters (glucose, total cholesterol, creatine kinase [median], and total protein) throughout the treatment-emergent period in the dupilumab and placebo groups.

The proportion of participants with PCSAs for metabolic parameters was low and similar between study intervention groups.

One participant (EFC16461 Study B, 18-30 age-group) in the dupilumab group with medical history of chronic gastritis and Gilbert’s syndrome had a PCSA of high creatine kinase level which was 711 IU/L at baseline and 1657 IU/L at Week 12 (normal range: 24 to 207). This PCSA was not considered as TEAE. The participant did not experience any TEAEs during the study. The creatine kinase level returned to normal at Week 24 (138 IU/L) and Week 36 (134 IU/L). Among the participants with baseline values in the normal range, the percentage of participants with PCSA in metabolic parameters was similar between intervention groups. No clinically meaningful trends were observed.

Individual clinically relevant abnormalities

No participants experienced abnormality in metabolic parameters that were considered treatment-emergent SAEs or TEAEs leading to permanent study intervention discontinuation.

Electrolytes

No clinically meaningful changes over time were observed in mean electrolyte levels (sodium, potassium, chloride, calcium, and bicarbonate) throughout the treatment-emergent period in the dupilumab and placebo groups.

Potentially clinically significant abnormality

There were no PCSAs for sodium, chloride, bicarbonates, nor calcium and there was 1 PCSA of low potassium and 1 PCSA of high potassium identified throughout the treatment-emergent period, in the dupilumab group.

Individual clinically relevant abnormalities

No participants experienced an electrolyte laboratory test abnormality that was considered SAE or TEAE leading to permanent study intervention discontinuation.

RENAL FUNCTION

No clinically meaningful changes over time were observed in mean renal function parameters (creatinine, blood urea nitrogen, urate, and creatinine clearance) throughout the treatment-emergent period in the dupilumab and placebo groups.

Potentially clinically significant abnormality

The proportion of participants with PCSAs for renal function parameters (regardless of baseline values) was low and similar between study intervention groups during the treatment-emergent period. The PCSAs for low, mild decrease in creatinine clearance (adults) were reported with a higher incidence in participants in the dupilumab group compared to the placebo group (10.7% versus 3.9%, respectively) among the participants with normal or missing value at baseline. Creatinine was elevated for only 1 participant in the placebo group; none of the participants in the dupilumab group had an elevated creatine, electrolyte abnormalities, abnormal urinalysis, or abnormal blood pressure. One participant in the dupilumab group had rhabdomyolysis prior to administration of first dose; second dose of dupilumab was held. After resolution of the rhabdomyolysis, the patient was continued on subsequent study intervention administration. For the 5 adolescents and 2 children (glomerular filtration rate data), there were no PCSAs identified.

Individual clinically relevant abnormalities

No participants experienced laboratory test abnormalities in renal function that was considered SAE or TEAE leading permanent intervention discontinuation.

LIVER FUNCTION

No clinically meaningful changes over time were observed in mean liver function parameters (ALT, AST, alkaline phosphatase, lactate dehydrogenase, total bilirubin, and albumin) throughout the treatment-emergent period in the dupilumab and placebo groups.

Potentially clinically significant abnormality

The number of participants with PCSAs for liver function parameters was low. No participants experienced a PCSA that met the criteria of ALT or AST >3×ULN and total bilirubin >2 x ULN.

Four participants in the dupilumab group (versus none in the placebo group) experienced a PCSA of high ALT, 2 participants with ALT >3×ULN and 2 participants with ALT >5×ULN. Two participants (both in EFC16461 Study A) had abnormal ALT values at baseline that were not reported as TEAEs: 1 participant with ALT >3×ULN (with baseline ALT at 4.18×ULN and baseline AST at 17.53×ULN and 1 participant with ALT >5×ULN (with baseline ALT at 5.33×ULN and baseline AST at 3.47×ULN). Their ALT and AST value returned to below 3×ULN before the last dose of study intervention. The 2 other participants had elevated ALT values that were also reported as TEAEs:

• One participant (EFC16461 Study B) with a baseline ALT of 2.40×ULN (screening ALT at 1.15×ULN then 0.73×ULN) had an elevated post-baseline ALT of 3.73×ULN at Week12, which recovered and returned to baseline status before the last dose of study intervention.

• One participant (EFC16461 Study A) with a baseline ALT of 2.35×ULN had an elevated post-baseline ALT of 5.03×ULN, which recovered and returned to baseline status before the last dose of study intervention.

Individual clinically relevant abnormalities

No participants experienced a liver function abnormality-related TEAE that was considered serious or leading to a permanent study intervention discontinuation. As per AESI criteria, there were no significant ALT increases. As per other selected AE groupings criteria, 4 participants (all in the dupilumab group, none in the placebo group) experienced nonserious potential drug-related hepatic disorders (ALT increase in 1 participant, hepatic steatosis in 1 participant, ALT increase and hepatic steatosis in 1 participant and ALT increase and AST increase in 1 participant).

Vital signs and physical findings

No clinically meaningful changes over time were observed for vital sign parameters (SBP, DBP, HR, weight, respiratory rate, body temperature) throughout the treatment-emergent period in the dupilumab and placebo groups.

Potentially clinically significant abnormality

In participants with normal or missing baseline vital signs, no post-baseline PCSAs were observed throughout the treatment-emergent period, except for 2 (1.8%) participants in the dupilumab group (of which 1 was also reported as nonserious TEAE)) and 1 (0.9%) participant in the placebo group with post-baseline PCSA for high and increase from baseline systolic blood pressure (≥160 mmHg and increase from baseline ≥20 mmHg). Thirty-six participants had weight related PCSA, of which 16 participants (7 [5.8%] in the dupilumab group and 9 [7.9%] in the placebo group) experienced notable weight losses (≥5% decrease from baseline) and 20 participants (11 [9.6%] in the dupilumab group and 9 [8.1%] in the placebo group) experienced notable weight gains (≥5% increase from baseline), but this was balanced between intervention groups.

Individual clinically relevant abnormalities

No participants experienced a TEAE related to abnormalities in vital signs that was considered serious or that led to permanent study intervention discontinuation. A post-baseline PCSA of "high and increase from baseline systolic blood pressure" was reported as a nonserious TEAE of hypertension in 1 participant in the dupilumab group (one participant in EFC16461 Study B; more details are provided in Section 3.1.1).

ECG

Potentially clinically significant abnormality

In EFC16461 Study B, the incidence of post-baseline PCSAs was <5% in the dupilumab group. In EFC16461 Study A, the incidence of post-baseline PCSAs was <5% in both intervention groups, except for PCSA of Grade 1 high QTc interval (4 [5.9%] in the dupilumab group and 5 [7.8%] in the placebo group). There were no Grade 3 PCSAs.

Individual clinically relevant abnormalities

There were no relevant ECG abnormalities that were reported as treatment-emergent SAEs or TEAEs leading to permanent intervention discontinuation.

2.5.8. Safety in special populations

Intrinsic factors

The following intrinsic factors were analyzed for their effects on the incidence of number of participants with any TEAEs, any treatment-emergent SAE, and any TEAE leading to study intervention discontinuation:

• Age group: <median, ≥median, <12 years, 12 to <18 years, 18 to <65 years, ≥65 years,

• Gender (male/female),

• Race (white/other races),

• Ethnicity (Hispanic or Latino/not Hispanic nor Latino),

• Baseline weight (</≥ to median baseline weight of 75 kg; </≥ to median baseline weight of 60 kg),

• Baseline BMI (<25, ≥25 to <30, ≥30),

• Baseline disease characteristics: prior omalizumab treatment (Yes, No), presence of angioedema (Yes, No), duration of disease (<2 years, 2 to 10 years, >10 years), UAS7 (<28, ≥28), ISS7 (<13, ≥13),

• Concomitant or background medications: H1-antihistamines 1-fold, >1-fold,

• Biomarkers: baseline total serum IgE: <median, ≥median, <100, ≥100 IU/L.

No meaningful differences were observed between subgroups including the subgroup by baseline severity (moderate [UAS7 <28] or severe [UAS7 ≥ 28]) (2.7.4 [Table 48] and [Table 49]).

Among the 6 adolescents (3 in the dupilumab group and 3 in the placebo group), no participants in the dupilumab group experienced any TEAE. There were 2 out of 3 adolescents in the placebo group who experienced TEAEs: asymptomatic COVID-19 in 1 participant and mild post procedural fever "due to COVID-19 vaccine injection" in 1 participant). There were no TEAEs reported in the 2 children enrolled in EFC16461 Study A.

Table 48. Overview of adverse event profile by baseline demographic subgroups: Treatment-emergent adverse events – Pooled safety population

Subgroup n (%)	Placebo (N=122)	Dupilumab (N=124)	Dupilumab vs placebo	
			Risk difference (95% CI)[a]	Hazard ratio (95% CI)[b]
Age group 1 (years)				
<43 (Median)	34/59 (57.6)	30/56 (53.6)	-0.04 (-0.21 to 0.14)	0.85 (0.52 to 1.41)
≥43 (Median)	35/63 (55.6)	41/68 (60.3)	0.05 (-0.12 to 0.21)	0.98 (0.62 to 1.54)
Age group 2 (years)				
<12	0/0	0/2	NC (NC to NC)	NC (NC to NC)
≥12-<18	2/3 (66.7)	0/3	-0.22 (-0.74 to 0.30)	0.00 (0.00 to NC)
≥18-<65	62/107 (57.9)	60/101 (59.4)	0.01 (-0.12 to 0.15)	0.94 (0.66 to 1.35)
≥65	5/12 (41.7)	11/18 (61.1)	0.14 (-0.18 to 0.47)	1.40 (0.47 to 4.13)

Subgroup n (%)	Placebo (N=122)	Dupilumab (N=124)	Dupilumab vs placebo	
			Risk difference (95% CI)[a]	Hazard ratio (95% CI)[b]
Gender				
Male	14/31 (45.2)	23/46 (50.0)	0.04 (-0.18 to 0.25)	0.88 (0.45 to 1.72)
Female	55/91 (60.4)	48/78 (61.5)	0.01 (-0.13 to 0.16)	0.97 (0.66 to 1.43)
Race				
White	48/89 (53.9)	53/90 (58.9)	0.05 (-0.10 to 0.19)	1.09 (0.74 to 1.61)
Other	20/32 (62.5)	17/32 (53.1)	-0.09 (-0.32 to 0.14)	0.55 (0.28 to 1.07)
Ethnicity				
Hispanic or Latino	7/19 (36.8)	12/20 (60.0)	0.19 (-0.09 to 0.48)	2.00 (0.78 to 5.16)
Not Hispanic or Latino	61/102 (59.8)	59/104 (56.7)	-0.03 (-0.16 to 0.10)	0.82 (0.57 to 1.18)
Baseline weight group 1 (kg)				
<75 (Median)	38/64 (59.4)	34/57 (59.6)	-0.01 (-0.18 to 0.16)	0.85 (0.53 to 1.35)
≥75 (Median)	30/57 (52.6)	37/67 (55.2)	0.02 (-0.15 to 0.19)	1.00 (0.62 to 1.62)
Baseline weight group 2 (kg)				
<60	17/24 (70.8)	12/23 (52.2)	-0.16 (-0.42 to 0.10)	0.57 (0.25 to 1.30)
≥60	51/97 (52.6)	59/101 (58.4)	0.06 (-0.08 to 0.19)	1.04 (0.72 to 1.52)
Baseline BMI group (kg/m^2)				
<25	27/47 (57.4)	27/49 (55.1)	-0.04 (-0.23 to 0.16)	0.79 (0.46 to 1.37)
≥25- < 30	18/34 (52.9)	22/35 (62.9)	0.09 (-0.13 to 0.32)	1.20 (0.64 to 2.26)
≥30	23/40 (57.5)	22/40 (55.0)	-0.02 (-0.23 to 0.18)	0.82 (0.45 to 1.47)
Region[c]				
Asia	16/23 (69.6)	12/23 (52.2)	-0.17 (-0.43 to 0.09)	0.33 (0.15 to 0.72)
Latin America	7/17 (41.2)	12/17 (70.6)	0.25 (-0.05 to 0.54)	2.34 (0.87 to 6.31)
Eastern Europe	13/23 (56.5)	15/22 (68.2)	0.11 (-0.16 to 0.37)	1.25 (0.59 to 2.64)
Western Countries	33/59 (55.9)	32/62 (51.6)	-0.04 (-0.21 to 0.13)	0.88 (0.54 to 1.44)
Territory[d]				
North America	23/43 (53.5)	22/47 (46.8)	-0.06 (-0.26 to 0.14)	0.87 (0.48 to 1.56)
European Union & United Kingdom	11/19 (57.9)	11/17 (64.7)	0.05 (-0.25 to 0.35)	1.06 (0.45 to 2.46)
Rest of World	35/60 (58.3)	38/60 (63.3)	0.04 (-0.12 to 0.21)	0.89 (0.56 to 1.42)

TEAE: Treatment-emergent adverse event, BMI: Body Mass Index

n (%) = number and percentage of participants with at least one AE out of the number of participants within the intervention group and subgroup level

a 95% confidence interval calculated using Miettinen and Nurminen method stratified by study.

b Calculated from Cox proportional hazards model with intervention in the model and stratified by study. Participants without an event were censored at end of treatment-emergent period.

c Asia: China and Japan; Latin America: Argentina; East Europe: Russia, Hungary; Western Countries: Canada, USA, France, Germany, Spain, United Kingdom

d North America: Canada, USA; European Union & United Kingdom: France, Germany, Hungary, Spain, United Kingdom; Rest of World: China, Japan, Argentina, Russia

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Table 49. Overview of adverse event profile with risk differences and hazard ratios (95% CI) by baseline disease characteristics subgroups: Treatment-emergent adverse events – Pooled safety population

Subgroup n (%)	Placebo (N=122)	Dupilumab (N=124)	Dupilumab vs placebo	
			Risk difference (95% CI)[a]	Hazard ratio (95% CI)[b]
Prior omalizumab treatment				
Yes	29/54 (53.7)	33/54 (61.1)	0.07 (-0.11 to 0.26)	1.13 (0.69 to 1.86)
No	40/68 (58.8)	38/70 (54.3)	-0.05 (-0.21 to 0.12)	0.78 (0.50 to 1.22)
Angioedema at baseline				
Yes	42/67 (62.7)	33/48 (68.8)	0.05 (-0.12 to 0.23)	1.08 (0.68 to 1.71)
No	27/55 (49.1)	38/76 (50.0)	0.01 (-0.16 to 0.18)	0.91 (0.56 to 1.50)
Baseline UAS7				
<28	23/42 (54.8)	19/32 (59.4)	0.04 (-0.18 to 0.26)	1.11 (0.61 to 2.05)
≥28	46/80 (57.5)	52/92 (56.5)	-0.01 (-0.15 to 0.14)	0.85 (0.57 to 1.27)
H1 antihistamine baseline dose				
1-fold	33/59 (55.9)	30/52 (57.7)	0.02 (-0.16 to 0.20)	1.04 (0.63 to 1.71)
>1-fold	36/62 (58.1)	41/72 (56.9)	-0.00 (-0.17 to 0.16)	0.81 (0.52 to 1.27)

TEAE: Treatment-emergent adverse event, UAS7: urticaria activity score over 7 days; ISS7: itch-severity score over 7 days

n (%) = number and percentage of participants with at least one AE out of the number of participants within the intervention group and subgroup level

a 95% confidence interval calculated using Miettinen and Nurminen method. The analyses were stratified by study except in the prior omalizumab treatment subgroups.

b Calculated from Cox proportional hazards model with intervention in the model. The analyses were stratified by study except in the prior omalizumab treatment subgroups. Participants without an event were censored at end of treatment-emergent period.

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Extrinsic factors

The following extrinsic factors were analyzed for their effects on the incidence of number of participants with any TEAEs, any treatment-emergent SAE, and any TEAE leading to study intervention discontinuation (2.7.4 [Table 48]):

• Region (Asia [China, Japan], Latin America [Argentina], Western Countries [Canada, US, France, Germany, Spain, United Kingdom], and East Europe [Hungary, Russia]),

• Territory (North America, European Union & United Kingdom, Rest of World).

No meaningful differences were observed between subgroups.

2.5.9. Immunogenicity

A detailed summary of immunogenicity in Phase 3 CSU program is provided in Table 50 for the treatment-emergent period including the follow-up time until week 36, and in Table 51 for the on-treatment period until week 24. The summary provides ADA incidences based on the type of ADA response and titer category identified in the ADA population.

During the entire study period, 19 participants treated with dupilumab and 3 participants treated with placebo had treatment-emergent ADA response. In the dupilumab group, 13 out of the 19 (68.4%) ADA-positive participants and 56 out of the 100 (56.0%) ADA-negative participants experienced at least 1 TEAE. Of the 22 participants with treatment-emergent positive ADA responses, 5 participants (all in the

dupilumab group) experienced TEAEs on or after the first identified ADA response, all in EFC16461 Study B. 4 out of 5 participants experienced TEAEs that are not usually associated with ADA-positive response and were assessed as not related to the study intervention by the Investigator: COVID-19

and persistent depressive disorder in 1 participant, cholelithiasis and hepatic steatosis in 1 participant, dysuria in 1 participant, and asymptomatic accidental overdose in 1 participant (2 consecutive IMP doses administered 10 days apart).

One of the participants had first identified ADA response (persistent and neutralizing ADA) and study intervention discontinuation for lack of efficacy on Day 29 (Week 4 visit) and was hospitalized for moderate chronic spontaneous urticaria ("generalized exacerbation of CSU") on Day 30 (treatment-emergent SAE). This participant received the last administration of study intervention on Day 16. The treatment-emergent SAE was assessed as not related to the study intervention by the Investigator. There was no significant impact of ADA formation on safety in these 22 participants with positive ADA responses. Overall, comparison of the frequencies of TEAEs during the study intervention period did not show meaningful differences between the ADA positive and ADA negative groups in the dupilumab and placebo groups.

Table 50. ADA incidence in Phase 3 studies in patients with CSU (EFC16461 Study B and Study A) through Week 36 (on-treatment period and follow up period)

Anti-dupilumab antibodies N (%)	EFC16461 Study A		EFC16461 Study B		Pool (Study A and Study B)	
	Placebo (N=66)	Dupilumab[a] (N=69)	Placebo (N=53)	Dupilumab[a] (N=52)	Placebo (N=119)	Dupilumab[a] (N=121)
Pre-existing ADA[b]	0 (0%)	1 (1.4%)	1 (1.9%)	1 (1.9%)	1 (0.8%)	2 (1.7%)
Treatment-emergent response[c]	1 (1.5%)	9 (13.0%)	2 (3.8%)	10 (19.2%)	3 (2.5%)	19 (15.7%)
Persistent response[d]	0 (0%)	3 (4.3%)	0 (0%)	5 (9.6%)	0 (0%)	8 (6.6%)
Indeterminate response[e]	0 (0%)	5 (7.2%)	0 (0%)	5 (9.6%)	0 (0%)	10 (8.3%)
Transient response[f]	1 (1.5%)	1 (1.4%)	2 (3.8%)	0 (0%)	3 (2.5%)	1 (0.8%)
Peak post-baseline titer						
Low (<1,000)	1 (1.5%)	9 (13.0%)	2 (3.8%)	8 (15.4%)	3 (2.5)	17 (14.0%)
Moderate (1,000-10,000)	0 (0%)	0 (0%)	0 (0%)	2 (3.8%)	0 (0%)	2 (1.7%)
High (>10,000)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Treatment-boosted response[g]	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Neutralizing antibodies	0 (0%)	8 (11.6%)	2 (3.8%)	8 (15.4%)	2 (1.7%)	16 (13.2%)

a Dupilumab dosing regimen: including both 300 mg q2w and 200 mg q2w regimens (see Table 1).
b Either an ADA-positive response in the ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline in the ADA assay with all post first dose ADA results less than 4-fold over baseline titer levels.
c A positive response in the ADA assay post first dose when baseline results are negative or missing.
d Treatment emergent ADA-positive response with two or more consecutive ADA-positive sampling time points separated by greater than 12-week period (greater than 84 days), with no ADA negative samples in between.
e Treatment-emergent response with only the last collected sample positive in the ADA assay.
f Treatment-emergent ADA-positive response that is not considered persistent or indeterminate.
g A positive response in the ADA assay post first dose that is greater than or equal to 4-fold over baseline titer levels, when baseline results are positive.

Source: 5.3.5.1 Studies EFC16461 Study A and Study B, Appendix 16.2.5 Compliance and drug concentration data [16.2.5.4.2.2.6] and [16.2.5.4.2.2.8]; 5.3.5.3 ISS Appendix 7 [7.2.1]

Table 51. ADA incidence in Phase 3 studies in patients with CSU (EFC16461 Study B and Study A) through Week 24 (on-treatment period)

Anti-dupilumab antibodies N (%)	EFC16461 Study A		EFC16461 Study B		Pool (Study A and Study B)	
	Placebo (N=66)	Dupilumab[a] (N=69)	Placebo (N=53)	Dupilumab[a] (N=52)	Placebo (N=119)	Dupilumab[a] (N=121)
Pre-existing ADA[b]	0 (0%)	1 (1.4%)	1 (1.9%)	1 (1.9%)	1 (0.8%)	2 (1.7%)
Treatment-emergent response[c]	0 (0%)	4 (5.8%)	1 (1.9%)	4 (7.7%)	1 (0.8%)	8 (6.6%)
Persistent response[d]	0 (0%)	0 (0%)	0 (0%)	1 (1.9%)	0 (0%)	1 (0.8%)
Indeterminate response[e]	0 (0%)	2 (2.9%)	1 (1.9%)	2 (3.8%)	1 (0.8%)	4 (3.3%)
Transient response[f]	0 (0%)	2 (2.9%)	0 (0%)	1 (1.9%)	0 (0%)	3 (2.5%)
Peak post-baseline titer						
Low (<1,000)	0 (0%)	4 (5.8%)	1 (1.9%)	3 (5.8%)	1 (0.8%)	7 (5.8%)
Moderate (1,000-10,000)	0 (0%)	0 (0%)	0 (0%)	1 (1.9%)	0 (0%)	1 (0.8%)
High (>10,000)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Treatment-boosted response[g]	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Neutralizing antibodies	0 (0%)	1 (1.4%)	1 (1.9%)	1 (1.9%)	1 (0.8%)	2 (1.7%)

a Dupilumab dosing regimen: including both 300 mg q2w and 200 mg q2w regimens (see Table 1).
b Either an ADA-positive response in the ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline in the ADA assay with all post first dose ADA results less than 4-fold baseline titer levels.
c A positive response in the ADA assay post first dose when baseline results are negative or missing.
d Treatment emergent ADA-positive response with two or more consecutive ADA-positive sampling time points separated by greater than 12-week period (greater than 84 days), with no ADA negative samples in between.
e Treatment-emergent response with only the last collected sample positive in the ADA assay.
f Treatment-emergent ADA-positive response that is not considered persistent or indeterminate.
g A positive response in the ADA assay post first dose that is greater than or equal to 4-fold over baseline titer levels, when baseline results are positive.

Source:PGM=PRODOPS/SAR231893/EFC16461/CSR_A3/EXPLO/PGM/a_pk_sum_ada_cat_a_t.sas
OUT=EXPLO/OUTPUT/a_pk_sum_ada_cat_a_t_i.rtf (27OCT2022 3:52)
PGM=PRODOPS/SAR231893/EFC16461/CSR_B4/EXPLO/PGM/a_pk_sum_ada_cat_a_t.sas
OUT=EXPLO/OUTPUT/a_pk_sum_ada_cat_a_t_i.rtf (27OCT2022 3:51)
PGM=PRODOPS/SAR231893/OVERALL/ISS_CSU_2021/EXPLO/PGM/a_pk_sum_ada_cat_a_t.sas
OUT=EXPLO/OUTPUT/a_pk_sum_ada_cat_a_t_i.rtf (26OCT2022 11:20)

2.5.10. Safety related to drug-drug interactions and other interactions

No new data are available on drug interactions.

2.5.11. Discontinuation due to adverse events

Overall, TEAEs leading to permanent study intervention discontinuation as per the Investigator's judgment were reported in 2 (1.6%) participants in the dupilumab group (including 1 treatment emergent SAE) and 4 (3.3%) participants in the placebo group (Table 52), all in EFC16461 Study A. All TEAEs that led to permanent intervention discontinuation occurred in 1 participant each. Except for the TEAE of arthritis experienced by 1 participant in the placebo group, all events were assessed as not related to the study intervention by the Investigator. All TEAEs (except for borderline personality disorder and the completed suicide) resolved and the pregnancy was completed by delivery without complication.

In the dupilumab group, TEAEs led to permanent intervention discontinuation in 2 participants: non-serious TEAE of borderline personality disorder and SAE of severe depression in one participant and pregnancy in one participant.

In the placebo group, in addition to the fatal event (one participant, completed suicide, see Section 3.1.4), there were moderate prurigo (one participant), moderate arthritis (one participant), and mild flare of CSU (one participant) that each led to study intervention discontinuation.

Table 52. Number (%) of participants with TEAE(s) leading to permanent study intervention discontinuation by Primary SOC and PT – Pooled safety population

Primary System Organ Class Preferred Term n (%)	Placebo (N=122)	Dupilumab (N=124)
Any event	4 (3.3)	2 (1.6)
Psychiatric disorders	1 (0.8)	1 (0.8)
Borderline personality disorder	0	1 (0.8)
Depression	0	1 (0.8)
Completed suicide	1 (0.8)	0
Skin and subcutaneous tissue disorders	2 (1.6)	0
Chronic spontaneous urticaria	1 (0.8)	0
Prurigo	1 (0.8)	0
Musculoskeletal and connective tissue disorders	1 (0.8)	0
Arthritis	1 (0.8)	0

2.5.12. Post marketing experience

No new safety concerns have been identified from the postmarketing data in the most recently submitted PBRER for dupilumab, which covered the period up to 28 Mar 2023. The MAH concludes that the benefit risk profile of dupilumab across all authorized indications as of 28 Mar 2023 remains favorable in the post-marketing setting.

2.5.13. Discussion on clinical safety

Studies

The submitted safety data were collected in two completed clinical studies, EFC16461 Study A and EFC16461 Study B.

Part A was a Phase 3, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of dupilumab in participants with CSU who remained symptomatic despite the use of H1-antihistamine and who were naïve to omalizumab.

Part B was a Phase 3, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of dupilumab in adult and adolescent participants with CSU who remained symptomatic despite the use of H1-antihistamine and who were intolerant or incomplete responders to omalizumab. Participants were considered as intolerant or incomplete responders to omalizumab if they were treated for CSU with at least 300 mg Q4W of omalizumab for at least 3 months with a minimum of 3 injections and had an inadequate response or were intolerant, resulting in treatment discontinuation. Pertaining to the claimed indication, study population B is more representative compared with study population A due to the pre-treatment. A comparison of adverse events across the CSU studies has been provided by the applicant, see below.

The study design of both parts was almost identical apart from the participant population in terms of the obtained pre-treatment (omalizumab-naïve vs. omalizumab-treated). Patients received the following weight-tiered dosing regimen which is approved for the AD and asthma indication: Adults and adolescents ≥ 60 kg Dupilumab were administered 300 mg or matching placebo Q2W following a

loading dose of 600 mg over a period of 24 weeks. Adolescents ≥ 30 kg received 200 mg matching placebo Q2W following a loading dose of 400 mg over the same time.

Data sources

The study population consisted of 246 participants, i.e. 108 participants enrolled in study B including 2 adolescents, and 138 participants enrolled in study A including 4 adolescents and 2 children. All participants who had received at least one dose of dupilumab weight-based regimen (124) or placebo (122) were included in the safety population, their pooled data was used for safety analyses. The pooling strategy is endorsed and was also applied throughout the previous approval procedures. Both study populations differed with respect to their pre-treatment, s.a.. Supportive safety data were submitted that originate from the post-marketing setting, from completed clinical studies in other approved indications, and from all new SUSARs from ongoing Phase 2/3/4 studies with data cut-off 29 September 2023.

Disposition and Exposure

As to the disposition of study participants, among all in the safety pool included patients the majority completed the 24-week intervention period. About 16% prematurely and permanently discontinued the study interventions due to lack of efficacy; most of these patients were assigned to the placebo group. It should be noted that both children assigned to the dupilumab groups discontinued the study drug following lack of efficacy. Overall, permanent study drug discontinuations due to adverse events occurred infrequently, especially in the dupilumab group.

The mean treatment compliance rate was high during both studies. In part B, critical or major protocol deviations were balanced between treatment groups, as well as in Part A. It is concurred that described protocol deviations unlikely impacted the presented study results.

The total exposure was slightly higher in the dupilumab group. According to the demographic characteristics the exposure was highest in female participants aged 18 to 64 years of Caucasian/White descent living in Western countries, and reasonably balanced between the subgroups of both studies.

The majority of study participants was exposed for ≥24 weeks. The exposure of paediatric participants, however, was dwindling small because only 6 (2.4%) adolescents and 2 (0.8%) children had been enrolled and treated in the studies. Considering the prevalence of CSU in the paediatric population, which ranges from 0.1-3% this number seems adequate, however, some articles suggest that the prevalence may be higher. Direct statements on the safety profile derived from the submitted study data can hardly be made. It is acknowledged that PDCO accepted this low patient number as set out in the compliance check report. Per se, extrapolation of safety data is difficult. Moreover, safety data collected from adolescents throughout all clinical dupilumab trials are also limited compared to the safety data base in adults. Nevertheless, the MAH provided an acceptable justification as regards the possible extrapolation of safety results from adults to the paediatric CSU population upon request (see Annex 2).

Elderly participants are deemed adequately represented considering the overall CSU prevalence, which is highest between 40 and 59 years and more common in women than in men; this is also reflected by demographic characteristics.

Baseline data were balanced between the intervention groups of the pooled safety population. Nearly half of it presented with angioedema at baseline which is typical feature of antihistamine-refractory severe CSU with longer disease duration. The medical history, comorbid conditions associated with CSU as well as prior medications were balanced between the 2 intervention groups. More than half of the participants received 2-fold of antihistamine standard dose at baseline. Almost all the patients

included in study B were incomplete responders to omalizumab and had a higher disease burden characterised by longer disease duration, a higher baseline AAS7 mean score, and a higher baseline proportion of high dose antihistamine use. Consistent with the pre-treatment, baseline IgE levels were lower in study A population. Thus, the study population represents patients with uncontrolled, moderate to severe CSU activity. As stated in the Clinical Summary, the most frequently used prior medication for reason other than CSU was levothyroxine sodium; levothyroxine use during the study has been clarified based on corrected participant numbers, thus, its use did not increase throughout the study (see Annex 2).

Adverse events

The percentage of participants with any treatment-emergent adverse event was very similar between the dupilumab group and the placebo group, most of the reported TEAEs were mild to moderate in severity. Severe TEAEs were rarely reported and less frequently observed in the dupilumab group, as well as the treatment-emergent serious adverse events and TEAEs leading to permanent study drug discontinuation. Common TEAEs by System Organ Class were balanced between treatment groups or lower in the dupilumab group, i.e. infections and infestations (DUP 21.8% vs. PBO: 21.3%), skin and subcutaneous tissue disorders (DUP 16.9% vs. PBO 19.7%), and general disorders and administration site conditions (DUP 10.5% vs. PBO 13.9%). At PT level, most frequently reported TEAEs in the dupilumab group with a difference of greater 1% as compared to placebo were injection site reaction, accidental overdose, pharyngitis, and hypertension. Injection site reactions are discussed below (AESI). The accidental overdoses were not associated with further adverse events. TEAEs of hypertension were reported few participants (DUP 2.4% vs. PBO 0.8%); these were considered unrelated to the study drug which is deemed plausible based on the provided information.

Treatment-related adverse events occurred less frequently in the dupilumab group (12.1% vs. 17.2% in the PBO group). Injection-related TEAEs were most frequently reported, however, they were balanced between both treatment groups. Severe TEAEs were also more frequently reported in the placebo group and the observed events were qualitatively similar.

No deaths were reported in the dupilumab treatment groups. In the placebo group of study EFC16461 Study A, one participant died following a suicide; he had a pre-existing medical history of alcoholism and depression for 3 years. It has been reasoned that enrolment of this participant did not constitute a major protocol violation.

Serious TEAEs occurred more frequently in the placebo group. One participant included in the dupilumab treatment group of study B experienced a SAE of moderate chronic spontaneous urticaria which led to permanent treatment discontinuation due to lack of efficacy. The remaining SAEs were considered unrelated to dupilumab treatment.

Treatment-emergent AESI were rarely reported in both treatment groups and totally balanced. Two systemic hypersensitivity reactions (non-serious moderate urticaria following COVID-19 vaccines) and two pregnancies occurred. One pregnancy occurred in the dupilumab group during study intervention, and one in the placebo group during the follow-up. No dedicated data on their outcome were provided.

Conjunctivitis events occurred rarely and were also balanced between treatment groups. No further eye-related AESI were observed.

Injection related reactions were slightly more frequent in the placebo group, whereas potential drug-related hepatic disorders were more frequently observed in the dupilumab groups: One event of mild alanine aminotransferase increase was reported that was assessed as dupilumab-related event and which resolved spontaneously without treatment interruption or corrective treatment. The other two cases were assessed as unrelated to the study drug and triggered by underlying risk factors. It is

acknowledged that mAbs are unlikely to cause drug-induced liver injury, however, an immune response may be generated by foreign epitopes. The MAH provided post-marketing data in regards to drug-induced liver toxicity which do not raise safety concerns (see Annex 2).

Injection-site reactions were more commonly observed in the placebo group, almost all events were deemed related to the study drug, mild, self-limiting and decreasing over time. No further EASI or selected TEAEs occurred.

In terms of separate study analyses, the overall incidence of TEAEs was comparable between Study B and Study A. Participants included in the dupilumab group of Study B, however, experienced more frequently CSU-related TEAEs compared with the placebo group (18.5% vs. 7.4%), which was not observed in Study A (8.6% vs. 19.1% in Study A). In both studies, most frequently observed TEAEs at PT level were CSU (study B) as well as CSU and angioedema (study A), respectively. CSU-related TEAEs were generally manageable by corrective treatment or rescue therapy. The MAH justified the observed imbalance in study B by the recalcitrant study population, i.e. a higher baseline disease activity of the participants, a higher baseline AAS7 score, and a higher baseline proportion of high dose H1-antihistamine and omalizumab use. Indeed, patients included in study B had a longer mean time since their first diagnosis of CSU, and a lower mean baseline total IgE consistent with prior omalizumab treatment; patients with angioedema had only a slightly higher baseline AAS7 score (mean) and baseline H1-antihistamine pretreatment up to 2-4-fold standard dose when comparing the dupilumab groups. The differences in baseline data did not sufficiently explain the varying study results of CSU-related TEAEs. As reasoned by the applicant, differences between treatment groups were not statistically significant, these TEAEs occurred early (by Week 12, range of 3 to 86 days) in the study intervention period and demonstrated ISS7 and HSS7 scores potentially indicative of complete efficacy response by Week 24 (see Annex 2).

Discontinuation of the study drug due to adverse events

There were slightly more participants assigned to the placebo group with any TEAE leading to permanent study intervention discontinuation compared with the dupilumab group. In the dupilumab group, 2 participants were discontinued due to psychiatric disorders and pregnancy, respectively. In the placebo group in addition to the fatal event (s.a.), TEAEs of CSU, prurigo, and arthritis led to study drug discontinuation.

Laboratory findings and vital signs

The mean blood eosinophil counts of participants assigned to the dupilumab group in study B peaked around week 24; the rise of eosinophils was of transient nature, a phenomenon that has been observed during development programs of approved indications. Post-baseline PCSA for high eosinophil count were thus slightly higher in the verum group but remained below the threshold for eosinophilia TEAEs (≥5 Giga/L) and were not associated with clinical symptoms, see also section 5.5.6, assessment of AESI. PCSAs for liver function parameters were rarely observed and a few patients had transient elevations of ALT that were, however, not associated with clinical symptoms. The renal function was unaffected by dupilumab throughout the studies. No further clinically meaningful changes were observed as to hematological or metabolic parameters or electrolytes.

No clinically relevant abnormalities were reported as to vital signs and physical examinations or ECG.

Immunogenicity

The overall incidence of treatment-emergent ADA through week 24 and 36, respectively, was comparable to those observed in adults during other development programs; paediatric participants tend to develop lower ADA titers, as to this, however, no dedicated data is available in the dossier. Most of the determined ADA titers were low, and no high titer response was observed. Overall, the

ADA responses were fairly balanced between the verum groups of both studies B and A. Only individual participants experienced TEAEs such as CSU, angioedema, and injection site reactions. No hypersensitivity reactions or anaphylaxis were observed. Overall, the immunogenic potential of dupilumab seems to remain low bearing in mind the limited participant numbers. Thus, no clear conclusion can be drawn on this topic, especially as regards the adolescent population.

Safety in the paediatric subgroup

Study A included paediatric patients from the aged ≥6 to <18 years, whereas study B enrolled paediatric participants aged ≥12 to <18 years. A mentioned above, sparse data is available from the paediatric study population as only 8 patients were included in the safety pool (study A: 4 adolescents and 2 children, study B: 2 adolescents).

Thus, no firm conclusion can be drawn on the available safety results. Based on the presented data, no TEAEs occurred in the 3 adolescents and 2 children that were assigned to the dupilumab group.

Other paediatric safety data is currently available from the Dupixent clinical development programmes of approved indications, i.e. AD and asthma, as well as from the post-marketing setting including a registry. The safety profile of the approved indications is hitherto relatively consistent between adults and paediatric patients as well as across the different indications.

ADR

Criteria determined for ADR assessment are endorsed. It is concurred that no new ADRs need to be included in section 4.8 of the SmPC.

Supportive data

The presented post marketing data do not raise concerns on the safety of dupilumab. Clinical data from other dupilumab approved indications revealed indication-specific safety aspects; conjunctivitis events and further eye-related disorders, herpes infections or eosinophilic conditions were not observed in the CSU population.

2.5.14. Conclusions on clinical safety

Based on the analysis of the provided safety data, no new safety concerns were identified and dupilumab appears to be well tolerated in study participants with CSU. So far, the presented safety data in adults are consistent with the hitherto known safety profile of dupilumab and no new ADR were identified that should be included in the Product Information. As comorbidities like AD and asthma share common pathophysiological mechanisms with specific endotypes of CSU, it can be assumed that the safety profile is consistent during long term use in adults and adolescents. All 'other concerns' are deemed to be resolved.

2.5.15. 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.

2.5.16. Direct Healthcare Professional Communication

Not applicable

2.6. Significance / Non-Conformity of paediatric studies

Not applicable

3. Risk management plan

The MAH has submitted an updated RMP version 11 with this application. This updated EU-RMP v11.0 is prepared to support the current application for the new indication of moderate to severe Chronic Spontaneous Urticaria (CSU) in adults and adolescents 12 years and older, who are symptomatic despite treatment with H1 Antihistamines (H1-AHs) and who are intolerant to or inadequately controlled by anti-IgE therapy. In addition, this EU-RMP v11.0 includes data relative to extension of Eosinophilic Esophagitis (EoE) in pediatric patients from 1 to 11 years of age relevant to ongoing procedure EMEA/H/C/004390/II/0081 in which an RMP update was requested by the CHMP Rapporteur.

The currently approved version of RMP is 9. The assessment of RMP v 10 relevant to COPD indication is pending.

The (main) proposed RMP changes in v11 vs v10 were the following:

- Part I: Addition of new indication CSU
- Module II SI: Addition of epidemiological data for CSU and EoE pediatric indications
- Module II SIII: Addition of CSU exposure data;
- Module II SIV: Addition of data relative to CSU and EoE pediatric indications;
- Module II SVII: Update of risk tables to include relevant to CSU and EoE paediatric indications

PRAC Rapporteur's Assessment comment on main changes in the RMP

Part I.

Product Overview

Proposed indication CSU has been included. In addition the Table has been amended to include Extension of Eosinophilic Esophagitis (EoE) in pediatric population from 1 to 11 years of age (under assessment in procedure EMEA/H/C/004390/II/0081). The amended wording for Eosinophilic Esophagitis (EoE) is:

DUPIXENT is indicated for the treatment of eosinophilic esophagitis in adults, and adolescents and children 1 year and older, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy (see section 5.1 of SmPC).

The final approved indication wording in the procedures including COPD indication should be reflected in the final RMP.

Part II

SI. Epidemiology of the indication(s) and Target population(s)

Epidemiological data for CSU has been provided in a separate table which is endorsed.

The final approved indication wording in the procedures including COPD indication should be reflected in the final RMP.

SIII. Clinical trial exposure

Clinical trials exposure data have been updated mainly to include CSU exposure data.

SIV. Population not studied clinical trials

Table 46 has been mainly updated relevant to CSU indication.

SVII. Identified and potential risks

Risk tables have been updated to include data relevant to CSU and EoE paediatric indications.

SVIII. Safety specifications

The Proposed safety specification in the RMP V 11:

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

Part III. Pharmacovigilance plan

This section remains unchanged.

Part VI Summary of risk management plan

The section has been updated with the proposed indications of two procedures, CSU indication and extension of EoE in paediatric population.

The final approved indication wording of the procedures including COPD indication should be reflected in the final RMP.

3.1. Overall conclusion on the RMP

☒The updated RMP v 11 is not acceptable. See below and RSI.

Final approved indication wording in each procedure including pending COPD indication should be reflected in the final RMP. In addition, DLP of the RMP should be amended to 29 SEP 2023 on page one of the RMP as data from the Study EFC15805 with a cut-off date of 29 September 2023 was included.

Moreover, the MAH is requested to discuss how the new patient groups covered by new indications (CSU, EoE) could support the additional PhV activities in place aimed to gather more safety data on dupilumab use in the youngest age group. A proposal should be made.

The MAH is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

4. Changes to the Product Information

As a result of this variation, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.

Currently there are some PI amendments requested in Procedure II/81. These should be taken on board once finished, therefore an alignment is requested herewith.

Some minor changes are also made to the PI to bring it in line with the current QRD template version 10.4, appropriate appendices and the stylistic matters. In addition, the current Annex of the excipient's guideline shall be reflected.

Please refer to Attachment 1, which includes some additional changes to the Product Information.

4.1.1. User consultation

The company provided a justification for not performing the consultation with target patient groups. The variation is related to the treatment of moderate to severe chronic spontaneous urticaria (CSU) in adults and adolescents 12 years of age and older, who are symptomatic despite treatment with H1 antihistamines and who are intolerant to or inadequately controlled by anti-IgE therapy, thus the following sections of the SmPCs of various presentations have been updated: section 4.1, 4.2, 4.8, 5.1, and 5.2.

Following these changes of the SmPC, the package leaflet needs to be adapted in section 1, 2 and 3.

The amendments in the package leaflet are minor and same wording is used as already user tested, the changes of the layout seem also minimal, thus the justification of the company is acceptable.

However, the key safety messages of the package leaflet will be affected due to the request of the inclusion of a warning statement related to polysorbate 80. This could be reflected in any next forthcoming variation.

4.1.2. Additional monitoring

Pursuant to Article 23(3) of Regulation No (EU) 726/2004, Dupixent (dupilimumab) has been removed from the additional monitoring list as new active substance.

4.1.3. Quick Response (QR) code

Not applicable.

5. Benefit-Risk Balance

5.1. Therapeutic Context

5.1.1. Disease or condition

Chronic spontaneous urticaria (CSU), also known as chronic idiopathic urticaria, is a skin disease characterized by the spontaneous appearance of pruritic wheals (hives) and flare-type skin reactions

without a specific known cause that persist for more than 6 weeks, and which may be accompanied by angioedema in approximately 40-50% of patients. Although all age groups can be affected, the peak incidence occurs between 20 and 40 years of age with women more frequently affected than men. Itch is the most predominant symptom in CSU. Severe itch and unpredictable occurrence of wheals and angioedema are responsible for limitations on daily life, deteriorating patients' performance at school and work, as well as causing psychiatric disorders in these patients. Significant exacerbations of chronic urticaria may result in emergency room visits and hospitalizations. The underlying pathologic mechanism for CSU is believed to be related to mast cell and basophil activation by both IgE mediated and non-IgE mediated mechanisms. The current treatment guidelines for the management of CSU recommend the use of non-sedating oral H1-antihistamines as first-line therapy. However, a substantial proportion of patients remain symptomatic even with high-dose antihistamines. Currently, the only licensed treatment in antihistamine-refractory patients with CSU (aged 12 years and older) is omalizumab, an anti-IgE treatment.

5.1.2. Available therapies and unmet medical need

CSU is a debilitating condition for which there are no curative treatments. Current therapeutic options help control and prevent symptoms of itch and urticaria. H1-antihistamines are the mainstay of therapy. The only other approved treatment for CSU in adolescents and adults is the anti-IgE treatment, omalizumab. The treatment approaches for CSU in children <12 years of age are similar to adults and adolescents. However, omalizumab (biologic) is not approved for treatment of pediatric patients with CSU aged <12 years. The current international guideline (initiated by the European societies European Academy of Allergology and Clinical Immunology [EAACI]/Global Allergy [GA2LEN]/and Asthma European Network European Dermatology Forum [EDF] in collaboration with the World Allergy Organization [WAO]) recommends a 4-step treatment approach to direct primary care physicians and specialists in the management of their patients with urticaria. This guideline recommends that in Step 1 the treatment starts with non-sedating H1-antihistamines at approved doses. If symptoms are inadequately controlled after 2 to 4 weeks, an increase in H1antihistamine dose up to 4-fold (unapproved dose) is recommended (Step 2). If symptoms still remain uncontrolled or are intolerable, omalizumab (anti-IgE) should be added (Step 3). Beyond this, Step 4 treatment options include add-on ciclosporin A or montelukast (leukotriene receptor antagonist) to H1-antihistamine. The treatment algorithm in the guideline is the same for adult and adolescent patients. New treatment option for CSU patients who are intolerant or incomplete responders to anti-IgE therapy are needed.

5.1.3. Main clinical studies

Data for clinical efficacy and safety are based on the results from two randomized, double-blind, parallel-group, multicenter, placebo-controlled, 24-week treatment studies (EFC16461 Study A and EFC16461 Study B). Both studies were conducted under one master protocol and enrolled patients with moderate-to-severe CSU who were symptomatic despite the use of H1-antihistamines and had either previously shown an inadequate response or intolerance to anti-IgE therapy with omalizumab (Study B), or have not received anti-IgE therapy before (omalizumab naïve; Study A). Study B was submitted as pivotal and Study A as supportive study for efficacy. Study B enrolled adult and adolescent patients aged ≥12 to <18 years while adult and pediatric patients aged ≥6 to <18 years were enrolled in Study A. For both studies, dupilumab 300 mg q2w, dupilumab 200 mg q2w, or placebo were evaluated in adult and adolescent patients (≥12 to <18 years of age). Patients were followed up until week 36. Supportive safety data from new SUSARs and from post-marketing surveillance for approved indications were included for safety analyses.

5.2. Favourable effects

In patients with an incomplete clinical response to omalizumab (Study B), a reduction in the key urticarial symptoms (i.e. itch and hives) as measured by change in UAS7 was observed at week 24. The LS mean decrease from baseline was -14.37 and -8.54 in the dupilumab and placebo group, respectively, with a LS mean difference of -5.83 (95% CI: -11.37, -0.30; p=0.0390). Symptom improvements were similarly driven by a reduction in itch and hive severity as seen by consistent reductions in the UAS7 subcomponents ISS7 and HSS7 (evaluated as secondary endpoints) and were consistent between participants with moderate or severe disease activity. Post-hoc analysis indicated an increased number of patients with categorical improvements in UAS7 (e.g. from severe to controlled disease) as compared to placebo.

In patients who were naïve to omalizumab (Study A), overall greater improvements in urticarial symptoms were observed. The LS mean decrease from baseline was -20.53 in the dupilumab group and -12.00 in the placebo group, respectively, with a LS mean difference of -8.53 (95% CI: -13.16; p=0.0003). Disease control (UAS7 ≤6) or complete resolution of CSU symptoms (UAS7=0), evaluated as secondary endpoint, was achieved in an increased number of participants in the dupilumab group as compared to placebo (45.7% vs. 23.5% (p=0.0075) and 31.4% vs. 13.2% (p=0.0199).

Similar changes as for the primary endpoint were observed for the patient-reported outcome measures CU-Q2oL, PGIC/PGIS and DLQI.

5.3. Uncertainties and limitations about favourable effects

Changes in UAS7 observed in incomplete omalizumab responders (Study B) did not reach a minimal important difference on a group-level. There is an apparent number of participants with improvements in the placebo arm, likely representing spontaneous remissions. Overall, the treatment response was heterogeneous with a distinct number of participants showing substantial or only minor UAS7 improvements but also worsening in symptoms in both treatment groups. On a patient-level, data suggest that meaningful symptom improvement have been achieved after treatment with dupilumab in a subset of patients but these results are limited due to the post-hoc nature of the analysis and are not especially compelling.

There is no independent support from a second trial in the same CSU patient population.

The interim analysis performed with ~80% of participants met the specified criteria for futility which was publicly declared. As the futility analysis was non-binding, it is agreed that from a technical perspective no type 1 error inflation occurred and in principle adequate type 1 error control was in place at both analyses. However, given that the decision was made to stop the study for futility, it is not considered possible to revert this decision and to consider the study finally successful. To license the treatment in the given indication based on post hoc analyses, the trial results need to be especially compelling and robust. The results are not considered robust given the data obtained for the remaining participants after the interim cut-off date were not consistent with the result obtained at the interim analysis showing a pronounced shift in the UAS7 treatment response indicating that clinical responses in CSU patients are very volatile and can change substantially by adding only 25 subjects (23% of all enrolled patients).

Given the overall heterogenous response characteristics in both studies and the notable number of participants with improvements in the placebo group, it can be anticipated that a considerable number of patients may not receive additional benefit with dupilumab. Due to the heterogeneity of the CSU disease, it is unclear whether the observed treatment effect can be linked to a certain CSU

subpopulation (such as partial or complete omalizumab non-responders) or CSU endotype (e.g. autoimmune CSU) as no data to discriminate these subgroups have been collected during the studies.

While symptom improvements for itch and hives were observed, there was no difference in improvements in the angioedema activity score (ASS7) between dupilumab and placebo.

Long-term efficacy data are missing as the treatment period in both studies was only 24 Weeks. No long-term extension studies were conducted for the new indication of CSU. In both studies, there was no clear loss of response in UAS7 or ISS7 and HSS7 after treatment discontinuation during the 12-week follow-up. It is uncertain whether long-term therapy with the proposed posology is needed to maintain improvements in CSU symptoms once a satisfactory clinical response is achieved. The need for continued therapy needs to be regularly assessed by the prescribing physician. This will be reflected in the SmPC.

5.4. Unfavourable effects

The percentage of participants who reported at least 1 TEAE was similar between treatment groups (DUP 57.3% vs. PBO 56.6%). The most frequently reported TEAEs by SOC (≥10%) in the dupilumab group as compared with placebo were infections and infestations (21.8% vs. 21.3%), skin and subcutaneous tissue disorders (16.9% and 19.7%), general disorders and administration site conditions (10.5% and 13.9%), and injury, poisoning, and procedural complications (11.3% and 6.6%).

The most frequently reported TEAEs by PT (≥2%) in the dupilumab group with a difference of greater 1% as compared to placebo were injection site reaction (4.0% vs. 2.5%), accidental overdose (3.2% vs. 1.6%), pharyngitis (2.4% vs. 0.8%), hypertension (2.4% vs. 0.8%), and alanine aminotransferase increased (2.4% vs. 0).

One participant with a medical history of psychiatric disorders assigned to the placebo group died following suicide. Treatment-emergent SAEs were reported in 4.0% (DUP) vs. 5.7% (PBO). One serious CSU and angioedema event were reported in the dupilumab group.

AESI occurred in 1.6% of the participants in each treatment group; in both groups one participant each experienced a systemic hypersensitivity reaction and became pregnant. Furthermore, injection site reactions were observed in 8.9% of the patients (DUP) vs. 10.7% (PBO) and the majority thereof was considered related to the study drug. Potential drug-related hepatic disorder was reported for 3.2% (DUP) vs. 0% (PBO) participants. Hypersensitivity events were observed in 0.8% of each treatment group.

Severe TEAEs occurred in 2.4% participants in the dupilumab group and in 4.1% participants in the placebo group.

TEAEs that were considered related to the study intervention by the investigator were reported in 12.1% participants in the dupilumab group vs. 17.2% participants in the placebo group. Most of the study intervention-related TEAEs were recorded in SOC injection site reactions HLT 7.3% (DUP) vs. 9.8% (PBO).

Treatment discontinuations caused by TEAEs were reported in 1.6% of the participants assigned to the dupilumab group and in 3.3% of those in the placebo group.

No new ADR were identified.

The incidence of ADAs was overall low without relevant impact on safety and efficacy.

5.5. Uncertainties and limitations about unfavourable effects

The overall percentages of recorded TEAEs in the safety pool were balanced across the treatment groups. The majority of observed common TEAEs were mild to moderate in severity, unrelated to the study intervention, and self-limiting or resolved with corrective treatment.

Qualitatively, the observed TEAEs were consistent with those reported in previous clinical development programmes. No deaths occurred in the dupilumab group. Serious adverse events were more frequently observed in the placebo group and each individual treatment-emergent SAE PT was reported only once in either of the treatment groups and considered unrelated.

Treatment-related TEAEs were more frequently observed in the placebo group, no specific cluster as to PTs is existent in both treatment groups.

Treatment-emergent AESIs were balanced in percentage terms between the treatment groups; injection site reactions were mostly considered related to the study drug, however, mild to moderate, decreased over time and resolved spontaneously. Eye-related adverse events were rarely observed and conjunctivitis events were also balanced across the treatment groups. No further AESIs were observed in the safety pool.

All the TEAEs leading to premature and permanent intervention discontinuation were less frequently reported in the dupilumab group and considered unrelated.

Overall, the paediatric data available do not reveal additional safety concerns not already seen in the children/adolescent/adult populations with AD, but it has to be highlighted that the numbers recruited are so limited that no direct conclusion on safety data can be drawn. As comorbidities like AD and asthma share common pathophysiological mechanisms with specific endotypes of CSU, it can be assumed that the safety profile is consistent during long term use in adults and adolescents.

5.6. Effects Table

Table 53. Effects Table for CSU (data cut-off: EFC16461 Study A - 05 Oct 2021; EFC16461 Study B -18 July 2022)

Effect	Short description	Unit	Treat DUPI 300 mg Q2W	Ctrl PBO	Uncertainties / Strength of evidence	References
Favourable Effects						
UAS7	Change from baseline in UAS7 at Week 24	Pts.	-14.37	-8.54	Study conducted in sought indication (incomplete omalizumab responders). Futility announced after interim analysis Clinically meaningful differences only in individual patients (post-hoc responder analysis).	ITT EFC16461 Study B
		Pts.	-20.53	-12.00	Overall supportive. Broader study population (omalizumab naïve) is not fully comparable with targeted indication.	ITT EFC16461 Study A
Unfavourable Effects						
TEAE	Injection site reactions	%	4.0	2.5	Known ADR, mild-to-moderate, transient	Safety population EFC16461 Study A and B
	SAE	%	4.0	5.7	No cluster as to PTs/HLTs	idem
	Death	%	0	0.008	Participant assigned to the PBO group	idem
Immuno-genicity	ADA Persistent response nAb	%	6.6 1.7	0 0.8	Not associated with TEAEs or loss of efficacy	idem

Abbreviations: ADA: antidrug antibodies, Ctrl: Control, DUPI: Dupilumab, HLT: High level term, PBO: placebo, PT: Preferred term, Pts: points, Q2W: biweekly, SAE: serious adverse events, TEAE: treatment-emergent adverse events, UAS7: urticarial activity score over 7 days

Notes: -

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

The burden for CSU patients is substantial, especially if the disease is not well controlled. While anti-IgE therapy (i.e. treatment with omalizumab) is effective in a substantial number of CSU patients, a distinct proportion of patients remains uncontrolled. Current treatment options for this patient group consist of short-term oral corticosteroids and additional other systemic immunosuppressive agents such as off-label ciclosporin A. However, these treatment options harbour serious safety issues particularly regarding their long-term use.

In incomplete omalizumab responders (Study B), treatment with dupilumab led to substantial improvements in urticaria symptoms with consistent reductions in itch and hives. The treatment effect was, however, heterogenous with distinct numbers of patients also improving under placebo treatment, reflecting the spontaneous and possible self-limiting nature of the disease. In addition, results obtained in participants after the interim cut-off date were not consistent with the results obtained at the interim analysis showing a pronounced shift in the UAS7 treatment response indicating that clinical responses in CSU patients are very volatile and may change substantially over time. Consequently, in Study B, a clinically meaningful difference compared to placebo was not reached on a group-level. A higher number of patients achieved clinically meaningful symptom improvements but these results are limited due to the post-hoc nature of the analysis and are not considered sufficiently compelling. Similar symptom improvements seen in omalizumab naïve patients (Study A) in principal support a beneficial treatment effect of dupilumab in CSU but potential specific pathological characteristics of incomplete omalizumab responders remain. Overall, the data provided show that substantial symptom improvement may only be achieved in certain patients potentially belonging to a distinct CSU subpopulation. However, it was not possible to identify this population more precisely with the available data. Given the heterogeneous response, there is a high risk of treatment failure with only a certain group of patients who may benefit from dupilumab treatment. There is no independent support from a second trial in the same CSU patient population. Overall, the treatment effect as observed in the pivotal Study B is considered not sufficiently robust to demonstrate efficacy of dupilumab in the sought indication.

As the futility analysis was non-binding, from a technical perspective no type 1 error inflation occurred and in principle adequate type 1 error control was in place at both analyses. However, given that the decision was made to stop the study for futility, it is considered not possible to revert this decision and to consider the study finally successful. Still, one may base the decision to license the treatment in the given indication on the trial. In this case, the trial results need to be especially compelling and robust which has, however, not been sufficiently demonstrated in Study B.

As immunomodulatory drug with a subcutaneous route of administration, the most relevant safety concerns associated with dupilumab treatment are systemic hypersensitivity including events with immunogenicity helminthic infections, eosinophilic conditions, and conjunctivitis and keratitis related events which predominantly occurred in atopic dermatitis patients. There were no reported events of anaphylactic reactions, one event of systemic hypersensitivity reaction was observed in either of the treatment groups. Participants who experienced TEAEs of infections were balanced across the treatment groups, especially no helminthic infections were reported. Conjunctivitis related events were balanced, no further eye-related events occurred. No events of clinically symptomatic eosinophilia were reported. Furthermore, the available immunogenicity data do not rise concerns. The observed treatment-emergent adverse events were predominantly mild to moderate and resolved without additional treatment.

The exposure of study participants included in this submission is considered sufficient. Only 6 adolescent participants were enrolled which is consistent with the PIP. However, no direct conclusion on CSU-specific safety results can be drawn for the paediatric population as numbers are very limited. Principally, the safety profile of Dupixent remains unaltered based on the presented data. As the studies are completed, no further long-term data explicitly for CSU patients are to be expected. Atopic diseases have been commonly reported in CSU patients, such as asthma, allergic rhinitis, AD and food allergy suggesting pathogenic similarities. Currently available long-term safety data in AD and asthma are therefore considered informative as regards the long-term safety and tolerability of dupilumab in the CSU patients. Based on this, it can be accepted that no further dedicated long-term safety data beyond routine pharmacovigilance will be collected.

5.7.2. Balance of benefits and risks

In conclusion, the safety data appear consistent with the hitherto known safety profile bearing in mind the limited exposure, especially of paediatric patients. Due to the limited adolescent data available, no direct conclusion on CSU-specific safety data collected during the clinical studies can be drawn. However, the pathophysiological and clinical features of CSU in adolescents as opposed to adults were sufficiently discussed by the applicant suggesting that there is sufficient similarity between both age groups that supports the safe use of dupilumab in the target population. The therapeutic need of dupilumab in CSU patients that are not controlled with anti-IgE therapy is acknowledged. Given the overall heterogenous and volatile response pattern observed in the pivotal trial and the futility stop at the interim analysis, the final trial results despite being statistically significant are not considered sufficiently robust to demonstrate a clear benefit for patients in the sought indication making the application not acceptable.

5.7.3. Additional considerations on the benefit-risk balance

None

5.8. Conclusions

The CHMP considers the overall B/R of Dupixent is negative.