25 January 2024
EMA/10608/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dupixent

International non-proprietary name: Dupilumab

Procedure No. EMEA/H/C/004390/P46/013

Note

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

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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	27 Nov 2023	27 Nov 2023	☐
☐	CHMP Rapporteur Assessment Report	03 Jan 2024	09 Jan 2024	☐
☐	CHMP members comments	15 Jan 2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	18 Jan 2024	n/a	☐
☒	CHMP adoption of conclusions:	25 Jan 2024	25 Jan 2024	☐

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1. Introduction

On 3rd October 2023, the MAH submitted a completed paediatric study for dupilumab, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study **EFC16720** (*A randomised, double-blind, placebo-controlled, multicentre, parallel-group study of dupilumab in patients with chronic inducible cold urticaria who remain symptomatic despite the use of H1-antihistamine treatment*) is part of a clinical development program to investigate the use of dupilumab in patients with chronic urticaria.

2.2. Information on the pharmaceutical formulation used in the study

An overview on administered study interventions including the pharmaceutical formulations is shown in the Table 1 below.

Table 1 - Overview of study interventions administered

ARM name	Dupilumab	Placebo
Intervention name	For adults and those adolescents ≥60 kg: Dupilumab 300 mg For adolescents ≥30 kg and <60 kg: Dupilumab 200 mg	For adults and those adolescents ≥60 kg: Placebo matching dupilumab 300 mg For adolescents ≥30 kg and <60 kg: Placebo matching dupilumab 200 mg
Type	Biological/Vaccine	Other
Dose formulation	• Dupilumab 300 mg: a 150 mg/mL dupilumab solution in a pre-filled syringe to deliver 300 mg in 2 mL. or • Dupilumab 200 mg: a 175 mg/mL dupilumab solution in a pre-filled syringe to deliver 200 mg in 1.14 mL.	• Placebo matching dupilumab 300 mg will be supplied as an identical formulation to the active 300 mg formulation without dupilumab, in a pre-filled syringe to deliver placebo in 2 mL. or Placebo matching dupilumab 200 mg will be supplied as an identical formulation to the active 200 mg formulation without dupilumab, in a pre-filled syringe to deliver placebo in 1.14 mL.
Unit dose strength(s)	300 mg or 200 mg	0 mg
Dosage level(s)	300 mg every 14 ±3 days after an initial loading dose of 600 mg or 200 mg every 14 ±3 days after an initial loading dose of 400 mg	0 mg every 14 ±3 days after an initial loading dose of 0 mg
Route of administration	Subcutaneous	Subcutaneous
Use	Experimental	Experimental
IMP and NIMP	IMP	IMP

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

Study number: EFC16720

Study title: A randomised, double-blind, placebo-controlled, multi-centre, parallel-group study of dupilumab in patients with chronic inducible cold urticaria who remain symptomatic despite the use of H1-antihistamine treatment.

Study initiation date: 10 December 2020 (first signed informed consent).

Study completion date: 20 April 2023 (last participant last visit).

The analyses presented in this report are based on the database lock date of 16 May 2023.

2.3.2. Clinical study

EFC16720

A randomised, double-blind, placebo-controlled, multi-centre, parallel-group study of dupilumab in patients with chronic inducible cold urticaria who remain symptomatic despite the use of H1-antihistamine treatment.

Description

The EFC16720 study was a 24-week, randomised, double-blind, placebo-controlled, parallel-group, multi-centre study to evaluate the use of dupilumab in adults and adolescents (≥12 to <18 years old) with cols urticaria (ColdU) who remain symptomatic despite the use of H1-antihistamines. The study mainly enrolled adult participants (74) while 8 adolescent participants (≥12 years to <18 years) were included.

Methods

Study participants

Participants were enrolled based on the following main criteria:

- ≥12 years to 80 years of age
- a diagnosis of primary acquired chronic inducible ColdU defined as recurrence of itchy wheals and/or angioedema due to cold for longer than 6 weeks prior to the screening visit
- a positive ice cube provocation test, ie, presenting at least a confluent hive/wheal on the exposed skin area, at screening and at time of randomisation
- use a study-defined H1-antihistamine as needed or regularly/daily for at least 1 month before screening visit.
- Uncontrolled disease defined as:
    - either urticaria control test (UCT) <12 at screening and randomisation or
    - documented medical history of cold exposure triggered anaphylaxis or oropharyngeal oedema within 6 months prior to the screening visit, or

- documented medical history of cold exposure triggered urticaria requiring emergency medical care visit or treatment with epinephrine within 6 months prior to the screening visit.

Study Design

The total duration of the study per participant was up to 40 weeks and included the following 3 periods:

- 1) Screening Period (2 to 4 weeks): assessment of participant's eligibility status before randomisation.
- 2) Randomised study intervention period (24 weeks), during which the participant was administered:
  - dupilumab tiered by weight: 300 mg q2w SC (with loading dose of 600 mg [2 injections of 300 mg]) in adults and adolescents ≥60 kg; or 200 mg q2w SC (with a loading dose of 400 mg [2 injections of 200 mg]) for adolescents ≥30 kg and <60 kg.
  - or matching placebo.
- 3) Follow-up period (12 weeks): monitoring of a participant's status after stopping the study intervention.

Treatments

The study participants received either weight-tiered dupilumab regimen or matching placebo (see Table 1 above).

Objectives and endpoints

The efficacy of dupilumab was assessed based on the proportion of participants with negative ice cube provocation test (negative ice cube provocation test is defined as an absence of a confluent hive/wheal at the entire skin site of exposure after ice cube provocation test) compared with placebo. ColdU signs and symptoms were evaluated, after the ice cube provocation test by the Investigator (hives/wheals intensity) and the participant (itch severity, skin pain, skin burning sensation). In addition, ColdU disease activity was assessed daily by the participant using the cold urticaria activity score (ColdUAS) questionnaire in an e-diary where the participant had to report his/her skin reactions (wheals and swelling), skin sensations (itching, burning, pain or feeling hot), if he/she had been in contact with cold temperatures that usually cause skin reactions, if he/she had avoided cold trigger, and overall symptoms severity. The study also assessed the effect of dupilumab on urticaria control, participants´ health-related quality of life (HRQoL) and overall health status, proportion of participants with cold urticaria requiring emergency medical care visit or treatment with epinephrine, and reduction of rescue therapy.

Table 2 - Objectives and endpoints of Study EFC16720

Objectives	Endpoints
Primary	
• To demonstrate the efficacy of dupilumab in adult and adolescent participants with primary acquired chronic inducible cold urticaria (ColdU) who remain symptomatic despite the use of an H1-antihistamine	• Proportion of participants with negative ice cube provocation test* at Week 24 compared with placebo *Negative ice cube provocation test is defined as the absence of a confluent hives/wheal at the entire skin site of exposure after ice cube provocation test[a].
Secondary	
• To demonstrate the efficacy of dupilumab on primary acquired chronic inducible ColdU disease control	• Change from baseline in urticaria control test (UCT 4-item) at Week 24 compared with placebo • Proportion of well-controlled participants (UCT ≥12) at Week 24 compared with placebo • Proportion of participants with an improvement of ≥3 in UCT 4- item from baseline to Week 24 compared with placebo.
• To demonstrate the efficacy of dupilumab on primary acquired chronic inducible ColdU local signs and symptoms (hives/wheals, itch, burning sensation and pain) after provocation test	• Change from baseline in local wheal intensity at the provocation site at Week 12 and Week 24 using the wheal intensity Likert scale ranging from 0 to 5 (clinician evaluation) compared with placebo • Change from baseline in local itch severity at the provocation site at Week 12 and Week 24 using the Peak Pruritus Numerical Rating Scale (NRS, score 0 to 10) (patient reported) compared with placebo • Change from baseline in local skin burning sensation at the provocation site at Week 12 and Week 24 using the peak burning sensation NRS (patient reported) compared with placebo • Change from baseline in local pain severity at the provocation site at Week 12 and Week 24 using the peak pain sensation NRS (patient reported) compared with placebo • Proportion of participants with negative ice cube provocation test at Week 12 compared with placebo
• To demonstrate the efficacy of dupilumab on primary acquired chronic inducible ColdU disease activity	• Change from baseline in cold urticaria signs and symptoms severity at Week 24 on cold exposure days as measured by ColdUAS, compared with placebo • Change from baseline in the proportion of cold urticaria sign and symptom free days at Week 24 on cold exposure days as measured by ColdUAS, compared with placebo

Objectives	Endpoints
• To demonstrate improvement in health-related quality-of-life and overall disease status and severity	• Change from baseline in health-related quality-of-life (HRQoL) as measured by Dermatology Life Quality Index (DLQI) in participants ≥16 years old, and in Children's Dermatology Life Quality Index (CDLQI) in participants ≥12 to <16 years old at Week 24 compared with placebo • Change from baseline in Cold Urticaria Quality of Life (ColdU-QoL) at Week 24 compared with placebo.
• To evaluate the ability of dupilumab in reducing the proportion of participants who require rescue therapy	• Proportion of participants receiving rescue therapy for primary acquired chronic inducible ColdU during the planned treatment period compared with placebo
• To evaluate the proportion of participants with cold exposure triggered urticaria	• Proportion of participants with cold exposure triggered urticaria requiring emergency medical care visit or treatment with epinephrine (at provocation test and/or at home)
• To evaluate safety outcome measures	• Percentages of participants experiencing treatment-emergent adverse events (TEAEs) or serious adverse events (SAEs)
• To evaluate immunogenicity of dupilumab	• Incidence of treatment-emergent antidrug antibodies (ADA) against dupilumab over time
Pharmacokinetic (PK)/Pharmacodynamic (PD)	
• To evaluate PK of dupilumab	• Functional dupilumab concentrations in serum and PK profile
• To evaluate PD effect of dupilumab	• Total immunoglobulin E over time.

a Provocation test reading time for all endpoints: 15 minutes after the ice cube application start = 5 minutes ice cube application plus 10 minutes after removal of ice cube

Sample size

The study was powered for the primary endpoint assessing the proportion of all participants (including adults and adolescents) with negative ice cube provocation test at Week 24.

The sample size was calculated based on assumptions obtained from an internal database:

1) The placebo group has a specified percentage of participants with negative ice cube provocation test at Week 24 and the dupilumab group has a percentage of participants with negative ice cube provocation test at Week 24
2) There is a drop-out rate of 10% in both groups
3) The statistical test is a Z test that is based on the difference of the 2 proportions with unpooled variance estimate and 2-sided 1% significance level.
4) Participants are equally randomised to the dupilumab group and the placebo group.

Based on the assumptions 39 participants per group (78 participants in total) were determined to provide 90% power to detect the difference of response rate in the dupilumab group and the response rate in the placebo group.

Randomisation and blinding (masking)

Participants were to be centrally assigned to randomised IMP using an interactive response technology (IRT). The study participants were to be randomised 1:1 and to receive either weight-tiered dupilumab

regimen or matching placebo. Randomisation was stratified by age (adolescent versus adult) and within adult group by country and background H1-antihistamine regular/daily use (Yes/No). The number of participants using H1-antihistamine as needed prior to study entry was estimated.

Dupilumab 300 mg/200 mg and placebo matching dupilumab 300 mg/200 mg were to be provided in identically matched 2 mL/1.14 mL pre-filled syringes that are visually indistinguishable for each dose. Whilst the study was double-blinded in terms of treatment with either dupilumab or placebo, it was 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 to be used for the different weight categories for adolescents.

Statistical Methods

Analysis population

The primary analysis population for the efficacy endpoints was the intent-to-treat (ITT) population defined as all randomised participants analysed according to the intervention group allocated by randomisation.

Primary analysis

The primary efficacy endpoint was analysed using the Cochran-Mantel-Haenszel test stratified by region (combined countries) and background H1-antihistamine regular/daily use (Yes/No). The comparison of the proportions of participants with negative ice cube provocation test at Week 24 between dupilumab and placebo was derived, and the corresponding odd ratios and the 95% CI was reported.

Analysis of secondary endpoints

Key secondary endpoints (change from baseline in local wheal intensity at the provocation site at Week 24 [wheal intensity Likert scale, clinical evaluation] and change from baseline in the proportion of cold urticaria sign and symptom free days at Week 24 on cold exposure days) were analysed using an analysis of covariance (ANCOVA) model with baseline value of the endpoint, study intervention group, region (combined countries), and background H1-antihistamine regular/daily use (Yes/No) as covariates, with intercurrent events and missing data being handled by a hybrid method of the worst-observation-carried-forward and multiple imputation.

The safety variables, including adverse events, laboratory parameters, vital signs, electrocardiogram, and physical examinations were summarized using descriptive statistics.

Missing data handling

For continuous endpoints, missing data due to lack of efficacy were imputed using worst-observation-carried-forward approach and missing data not due to lack of efficacy were imputed using a multiple imputation method, which used all participants except those who had taken the highly influential prohibited medications and/or highly influential rescue medications and excluding patients who discontinued due to lack of efficacy. For binary endpoints, missing data were considered as non-responder.

In addition to the missing data handling approaches specified above, the reason and pattern of missing data were carefully examined, and tipping point analyses and additional sensitivity analyses were performed.

Multiplicity considerations

A multiplicity hierarchical testing was proposed to control the overall Type 1 error rate for testing the primary endpoint, selected patient-reported outcome(s) and the other key secondary endpoints. The study was to be considered positive when the primary endpoint achieved statistical significance.

Results

Participant disposition

Overall population

A total of 82 participants (including 8 adolescents) were randomised to study intervention: 42 in the dupilumab group and 40 in the placebo group. 41 participants were screen failures. The 3 main reasons for screen failure were inclusion criteria I03 (positive ice cube provocation test) not met (13.8% of participants screened), I04 (criteria of severity) not met (4.1%), and exclusion criterion E28 (participant not suitable for participation as judged by the Investigator) met. All randomised participants were exposed.

In the randomised population, 61 (74.4%) participants completed the 24-week study intervention period. The percentage of participants who permanently discontinued study intervention was high (25.6%) and similar between intervention groups (26.2% in the dupilumab group and 25.0% in the placebo group). The reported reasons for permanent study intervention withdrawal were withdrawal by subject (9 [21.4%] participants in the dupilumab group and 8 [20.0%] in the placebo group) and lack of efficacy (2 [4.8%] and 2 [5.0%]). A total of 63 (76.8%) participants completed the study (ie, the entire study intervention and post-intervention follow-up periods) and 19 (23.2%) participants discontinued from the study.

Adolescents

Among the 8 adolescents aged ≥12 years to <18 years, 4 were randomised in the dupilumab group (3 received dupilumab 300 mg [body weight at screening of 66.5 kg, 87.0 kg, and 74.0 kg] and 1 received dupilumab 200 mg [body weight at screening of 54.0 kg) and 4 in the placebo group. All adolescent participants completed the study intervention period except 1 participant in the placebo group who discontinued study intervention for lack of efficacy after Week 10 administration.

Baseline data

Overall population

The mean (SD) age of the randomised population was 35.4 (14.9) years (range: 12 to 73 years), 19 (23.2%) participants were male and 63 (76.8%) were female, and most of them were white (85.4%). The mean (SD) body weight was 73.76 (19.42) kg, with 24.4% of participants <60 kg and 75.6% ≥60 kg). Baseline disease characteristics were indicative of active and uncontrolled disease despite cold avoidance and use of H1-antihistamines, with the majority of participants having moderate ColdU disease. In total, 47.6% of participants had positive allergic medical history; however, consistent with exclusion criteria, no enrolled participant had active atopic dermatitis or ongoing chronic spontaneous urticaria, or other chronic inducible urticaria.

Adolescents

The demographics, participant characteristics, and disease characteristics at baseline of adolescent participants are provided in the tables below.

Table 3 - Demographics and participant characteristics at baseline - Adolescents in Randomised population

	Placebo (N=4)	Dupilumab (N=4)	All (N=8)
Age (years)			
Number	4	4	8
Mean (SD)	13.5 (2.4)	14.8 (1.3)	14.1 (1.9)
Median	12.5	15.0	14.0
Q1 ; Q3	12.0 ; 15.0	14.0 ; 15.5	12.5 ; 15.5
Min ; Max	12 ; 17	13 ; 16	12 ; 17
Region[a] [n (%)]			
Number	4	4	8
Asia	0	1 (25.0)	1 (12.5)
Latin America	1 (25.0)	1 (25.0)	2 (25.0)
Western Countries	3 (75.0)	2 (50.0)	5 (62.5)
Sex [n (%)]			
Number	4	4	8
Male	2 (50.0)	1 (25.0)	3 (37.5)
Female	2 (50.0)	3 (75.0)	5 (62.5)
Race [n (%)]			
Number	4	4	8
White	4 (100)	3 (75.0)	7 (87.5)
Black or African American	0	0	0
Asian	0	1 (25.0)	1 (12.5)
Japanese	0	1 (25.0)	1 (12.5)
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaska Native	0	0	0
Multiple	0	0	0
Not reported	0	0	0
Unknown	0	0	0
Ethnicity [n (%)]			
Number	4	4	8
Hispanic or Latino	0	0	0
Not Hispanic or Latino	4 (100)	4 (100)	8 (100)
Not reported	0	0	0
Weight (kg)			
Number	4	4	8
Mean (SD)	58.35 (27.20)	70.38 (13.82)	64.36 (20.98)
Median	59.55	70.25	70.25
Q1 ; Q3	35.10 ; 81.60	60.25 ; 80.50	46.95 ; 81.60
Min ; Max	30.3 ; 84.0	54.0 ; 87.0	30.3 ; 87.0
Weight group (kg) [n (%)]			
Number	4	4	8
<60	2 (50.0)	1 (25.0)	3 (37.5)
≥60	2 (50.0)	3 (75.0)	5 (62.5)
BMI (kg/m^2)			
Number	4	4	8
Mean (SD)	21.35 (6.54)	25.85 (6.38)	23.60 (6.45)
Median	21.45	24.54	23.43

	Placebo (N=4)	Dupilumab (N=4)	All (N=8)
Q1 ; Q3	15.84 ; 26.85	20.78 ; 30.92	18.80 ; 27.96
Min ; Max	14.4 ; 28.1	20.3 ; 34.0	14.4 ; 34.0
BMI group (kg/m^2) [n (%)]			
Number	4	4	8
<30	4 (100)	3 (75.0)	7 (87.5)
≥30	0	1 (25.0)	1 (12.5)

BMI: Body mass index

a Asia: Japan; Latin America: Argentina; Western Countries: Canada, USA, Germany.

Table 4 - Disease and other characteristics at baseline - Adolescents in Randomised population

	Placebo (N=4)	Dupilumab (N=4)	All (N=8)
Age at onset of cold urticaria (years)			
Number	4	4	8
Mean (SD)	10.0 (3.4)	10.5 (3.0)	10.3 (3.0)
Median	11.5	12.0	12.0
Q1 ; Q3	8.0 ; 12.0	9.0 ; 12.0	8.5 ; 12.0
Min ; Max	5 ; 12	6 ; 12	5 ; 12
Duration of cold urticaria before screening visit (years)[a]			
Number	4	4	8
Mean (SD)	3.8 (2.8)	4.8 (3.1)	4.3 (2.8)
Median	3.5	4.1	4.1
Q1 ; Q3	1.5 ; 6.0	2.6 ; 7.0	2.0 ; 6.0
Min ; Max	1 ; 7	2 ; 9	1 ; 9
Duration of cold urticaria before screening visit group (years)[a] [n (%)]			
Number	4	4	8
<5	2 (50.0)	2 (50.0)	4 (50.0)
5-10	2 (50.0)	2 (50.0)	4 (50.0)
>10	0	0	0
Number of patients who had cold urticaria events within 12 months before screening visit [n (%)]			
Number	0	0	0
Requiring hospitalization/emergency care	0	0	0
Requiring epinephrine	0	0	0
Requiring OCS	0	0	0
Resulting in anaphylactic reaction	0	0	0
Resulting in oropharyngeal oedema	0	0	0
Did the patient experience in past any of the following urticaria symptoms? [n (%)]			
Number	4	4	8
Localized skin urticaria	4 (100)	3 (75.0)	7 (87.5)
Generalized skin urticaria	3 (75.0)	2 (50.0)	5 (62.5)
Localized angioedema, including oropharyngeal	1 (25.0)	2 (50.0)	3 (37.5)
Generalized angioedema	0	1 (25.0)	1 (12.5)
Other systemic reactions	1 (25.0)	0	1 (12.5)

	Placebo (N=4)	Dupilumab (N=4)	All (N=8)
Respiratory distress	1 (25.0)	0	1 (12.5)
Hypotension	0	0	0
Gastrointestinal discomfort	0	0	0
Other	0	0	0
History of allergy[b]			
Number	4	4	8
Allergic	3 (75.0)	4 (100)	7 (87.5)
Non-Allergic	1 (25.0)	0	1 (12.5)
History of angioedema			
Number	4	4	8
Yes	1 (25.0)	2 (50.0)	3 (37.5)
No	3 (75.0)	2 (50.0)	5 (62.5)
Baseline Wheal intensity Likert scale			
Number	4	4	8
Mean (SD)	3.0 (1.4)	3.3 (1.3)	3.1 (1.2)
Median	2.5	3.0	3.0
Q1 ; Q3	2.0 ; 4.0	2.5 ; 4.0	2.0 ; 4.0
Min ; Max	2 ; 5	2 ; 5	2 ; 5
Baseline Peak pruritus NRS			
Number	4	4	8
Mean (SD)	6.0 (3.6)	5.8 (1.9)	5.9 (2.6)
Median	5.5	6.5	6.5
Q1 ; Q3	3.0 ; 9.0	4.5 ; 7.0	3.0 ; 7.5
Min ; Max	3 ; 10	3 ; 7	3 ; 10
Baseline number of cold exposure days as measured by ColdUAS[c]			
Number	4	4	8
Mean (SD)	11.3 (2.8)	9.5 (4.8)	10.4 (3.7)
Median	11.5	10.5	11.0
Q1 ; Q3	9.0 ; 13.5	6.0 ; 13.0	8.5 ; 13.5
Min ; Max	8 ; 14	3 ; 14	3 ; 14
Baseline proportion (%) of cold urticaria sign and symptom free days on cold exposure days as measured by ColdUAS[c, d]			
Number	4	4	8
Mean (SD)	6.3 (12.5)	0.0 (0.0)	3.1 (8.8)
Median	0.0	0.0	0.0
Q1 ; Q3	0.0 ; 12.5	0.0 ; 0.0	0.0 ; 0.0
Min ; Max	0 ; 25	0 ; 0	0 ; 25
Baseline cold urticaria signs and symptoms severity on cold exposure days as measured by ColdUAS[c]			
Number	4	4	8
Mean (SD)	3.6 (2.0)	3.3 (1.4)	3.5 (1.6)
Median	3.7	3.4	3.4
Q1 ; Q3	2.0 ; 5.2	2.3 ; 4.4	2.2 ; 4.8
Min ; Max	1 ; 6	2 ; 5	1 ; 6

	Placebo (N=4)	Dupilumab (N=4)	All (N=8)
Baseline UCT			
Number	4	4	8
Mean (SD)	6.0 (4.2)	5.0 (3.7)	5.5 (3.7)
Median	7.5	5.5	6.0
Q1 ; Q3	3.0 ; 9.0	2.5 ; 7.5	2.5 ; 9.0
Min ; Max	0 ; 9	0 ; 9	0 ; 9
Baseline DLQI score			
Number	1	1	2
Mean (SD)	7.0 (NC)	4.0 (NC)	5.5 (2.1)
Median	7.0	4.0	5.5
Q1 ; Q3	7.0 ; 7.0	4.0 ; 4.0	4.0 ; 7.0
Min ; Max	7 ; 7	4 ; 4	4 ; 7
Baseline CDLQI score			
Number	3	3	6
Mean (SD)	14.33 (12.66)	9.00 (6.56)	11.67 (9.48)
Median	12.00	8.00	10.00
Q1 ; Q3	3.00 ; 28.00	3.00 ; 16.00	3.00 ; 16.00
Min ; Max	3.0 ; 28.0	3.0 ; 16.0	3.0 ; 28.0
Screening ACUSI categorical score [n (%)]			
Number	4	3	7
4-7 (Mild ACU)	2 (50.0)	1 (33.3)	3 (42.9)
8-11 (Moderate ACU)	1 (25.0)	2 (66.7)	3 (42.9)
12-15 (Severe ACU)	1 (25.0)	0	1 (14.3)
Worst problems ever caused by cold urticaria [n (%)]			
Number	4	3	7
Hive, redness or itching	4 (100)	2 (66.7)	6 (85.7)
Deep swelling of the skin or mucous membranes/Angioedema	0	1 (33.3)	1 (14.3)
Circulatory complaints/Dizziness/Difficulty swallowing/Difficulty breathing	0	0	0
Unconsciousness/Shock	0	0	0
Baseline Total IgE (IU/mL)			
Number	3	4	7
Mean (SD)	630.67 (439.06)	1762.75 (1101.37)	1277.57 (1018.30)
Median	472.00	1686.00	894.00
Q1 ; Q3	293.00 ; 1127.00	823.50 ; 2702.00	472.00 ; 2478.00
Min ; Max	293.0 ; 1127.0	753.0 ; 2926.0	293.0 ; 2926.0
Baseline H1-antihistamine use [n (%)]			
Number	4	4	8
Regular/daily use	2 (50.0)	4 (100)	6 (75.0)
Per-need use	2 (50.0)	0	2 (25.0)
Baseline H1-antihistamine dose if regular/daily use [n (%)]			
Number	2	4	6
<1-fold	0	0	0
1-fold	1 (50.0)	2 (50.0)	3 (50.0)

	Placebo (N=4)	Dupilumab (N=4)	All (N=8)
2-fold to 3-fold	1 (50.0)	2 (50.0)	3 (50.0)
4-fold	0	0	0
Prior cold urticaria medication use [n (%)]			
Number	1	1	2
Leukotriene receptor antagonists (LTRAs)	0	1 (100)	1 (50.0)
H2-blockers	1 (100)	0	1 (50.0)
Omalizumab	0	0	0

OCS: oral corticosteroids; UCT: urticaria control test; NRS: numerical rating scale; ColdUAS: cold urticaria activity score; DLQI: Dermatology Life Quality Index; CDLQI: Children's Dermatology Life Quality Index; ColdU-QoL: Cold Urticaria Quality of Life; PGIS: participant global impression of severity; ACUSI: Acquired Cold Urticaria Severity Index; EQ-5D-5L: 5-level EuroQol 5-dimensional questionnaire; EQ-VAS: EuroQol visual analogue scale.

a Derived as (Year of screening visit - Year of first diagnosis of cold urticaria) + (month of screening visit - month of first diagnosis of cold urticaria)/12

b Defined as having a medical history of chronic spontaneous urticaria, angioedema (not related to cold urticaria), atopic dermatitis, allergic rhinitis, allergic conjunctivitis, asthma, food allergy, chronic sinusitis, nasal polyps or eosinophilic esophagitis.

c The ColdUAS related assessments were conducted during each 14 days window. The e-diary completion days should be ≥6 and cold exposure days should be ≥1 in the 14 days window, otherwise the assessment result is set to missing.

d Proportion of cold urticaria sign and symptom free days = sign and symptom free days/cold exposure days in 14 days window *100

Note: A low score indicates good outcome for Wheal intensity Likert scale (range 0-5), Peak pruritus NRS (range 0-10), Peak pain NRS (range 0-10), Peak burning sensation NRS (range 0-10), cold urticaria signs and symptoms severity on cold exposure days (range 0-6), DLQI/CDLQI (range 0-30), ColdU-QoL (range 0-100), PGIS (range 1-4), and ACUSI (rang 4-15); A high score indicates good outcome for UCT (range 0-16) and EQ-VAS (range 0-100).

Number analysed

A total of 82 participants were included in the efficacy and safety population. There were no participants excluded from the efficacy population (ITT population) nor from the safety population. One participant (randomised to the placebo group) incorrectly received dupilumab once, on Day 1 and was thus included in the dupilumab safety population.

Table 5 - Analysis populations in study EFC16720

n (%)	Placebo	Dupilumab	All
Randomized population	40 (100)	42 (100)	82 (100)
Efficacy population			
Intent-to-Treat (ITT)	40 (100)	42 (100)	82 (100)
ADA population	36	38	74
Pharmacokinetic (PK) population	0	38	38
Safety population	39	43	82
Population without trial impact (disruption) due to COVID-19	37 (92.5)	42 (100)	79 (96.3)

Note: For the safety, ADA and PK populations, participants are tabulated according to study intervention actually received (as treated).
For the other populations, participants are tabulated according to the study intervention allocated by randomization.

Efficacy results

Overall population

The study did not meet the primary endpoint and did not demonstrate a statistically significant difference in the proportion of participants with a negative ice cube provocation test (17 [40.5%] in the dupilumab group versus 15 [37.5%] in the placebo group; OR: 1.03, p=0.9492).

Dupilumab treatment did not show statistically significant improvement versus placebo across key secondary and other multiplicity-adjusted secondary endpoints that evaluated key components of ColdU, including hives and itch (as measured by local wheal intensity Likert scale and local itch severity peak pruritus NRS at ice cube provocation site, and ColdUAS over 14 days), or QoL (as measured by DLQI). In daily cold urticaria signs and symptoms measured by ColdUAS, a numerical difference was observed in favour of the dupilumab group as compared to the placebo group in proportion of cold urticaria signs and symptoms free days. However, given the amount of missing data (data imputed in 40% of participants in the dupilumab group and 30% of participants in the placebo group), no conclusion can be drawn.

- For reduction in local wheal intensity from baseline at Week 24 (a key secondary endpoint), the LS mean difference versus placebo was -0.03, with 95% CI: -0.72, 0.66 (p=0.9375).
- For increase in proportion of cold urticaria signs and symptoms free days on cold exposure days from baseline at Week 24 (a key secondary endpoint), the LS mean difference versus placebo was +12.16, with 95% CI: -5.81, 30.12 (p=0.1846).
- For reduction in local itch severity from baseline at Week 24, the LS mean difference versus placebo was -0.24, with 95% CI: -1.82, 1.33 (p=0.7598).
- For improvement in quality of life from baseline at Week 24, the LS mean difference versus placebo was +0.39, with % CI: -2.33, 3.11 (p=0.7798).

A trend to numerical difference was observed in cold urticaria signs and symptoms severity on cold exposure days (a secondary endpoint, not multiplicity-adjusted) with similar limitations related to the amount of missing data as the proportion of cold urticaria signs and symptoms free days.

Adolescents

Among the 8 adolescents, 3 out of 4 participants in the dupilumab group and 3 out of 4 participants in the placebo group had negative ice cube provocation test at Week 24, with improved Wheal intensity Likert scale compared to baseline. No difference in efficacy was observed between placebo and dupilumab in adolescents.

Table 6 - Summary of the primary and selected secondary endpoints in the hierarchical testing procedure – ITT population

Parameter	Placebo[a] (N=40)	Dupilumab[a] (N=42)	Difference (95% CI)[b] for Dupilumab vs. Placebo	Difference (99% CI)[b] for Dupilumab vs. Placebo	P-value[c]
Primary endpoint					
Proportion of participants with negative ice cube provocation test at Week 24	15 (37.5)	17 (40.5)	0.68 (-20.20, 21.56)	0.68 (-26.76, 28.12)	0.9492
Odds ratio			1.03 (0.41, 2.56)	1.03 (0.31, 3.41)	
Key secondary endpoints					
Change from baseline in wheal intensity Likert scale at the provocation site at Week 24	-1.52 (0.28)	-1.55 (0.27)	-0.03 (-0.72, 0.66)	-0.03 (-0.93, 0.88)	0.9375
Change from baseline in proportion of cold urticaria sign and symptom free days at Week 24 on cold exposure days over 14 days observation period	15.66 (7.49)	27.82 (7.26)	12.16 (-5.81, 30.12)	12.16 (-11.48, 35.79)	0.1846
Other Secondary endpoints					
Change from baseline in peak pruritus NRS at the provocation site at Week 24	-2.18 (0.63)	-2.43 (0.62)	-0.24 (-1.82, 1.33)	-0.24 (-2.31, 1.82)	0.7598
Change from baseline in HRQoL as measured by DLQI at Week 24[d]	-4.70 (1.08)	-4.32 (1.00)	0.39 (-2.33, 3.11)	0.39 (-3.20, 3.97)	0.7798

CMH: Cochran-Mantel Haenszel; NRS: numerical rating scale; ColdUAS: cold urticaria activity score; DLQI: Dermatology Life Quality Index.

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

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

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

d Excludes 6 adolescents who completed CDLQI.

Note: A low score indicates good outcome for Wheal intensity Likert scale (range 0-5), Peak pruritus NRS (range 0-10) and DLQI (range 0-30).

Safety results

Exposure

In the dupilumab group, 41 out of 42 participants received dupilumab 300 mg q2w, including 3 adolescents (with body weight ≥60 kg at screening). In addition, 1 adolescent with body weight <60 kg at screening received dupilumab 200 mg q2w. Of note there was 1 additional adult participant from the placebo group who was exposed to dupilumab (incorrectly received 1 injection of dupilumab 300 mg instead of placebo once, on Day 1).

The cumulative exposure to IMP (dupilumab or placebo) was numerically slightly longer in the dupilumab group (17.8 patient-years) than in the placebo group (15.8 patient-years). The median duration of study intervention exposure was 169.0 days in the dupilumab group and in the placebo group. More than a half of participants in both intervention groups received study intervention for the entire 24-week treatment period, with 65.1% in the dupilumab group and 64.1% in the placebo group receiving the maximum of 13 injections (including 2 injections for the loading dose); 95.3% in the dupilumab group and 94.9% in the placebo group were exposed to study intervention for at least 12 weeks.

All adolescents completed the study intervention and follow-up periods, except 1 participant in the placebo group who had an early study intervention discontinuation after Week 10 administration for lack of efficacy.

Adverse events

Overall population

An overview of the adverse event profile observed in study EFC16720 is shown in the Table 7 below.

Table 7 - Overview of adverse event profile: Treatment-emergent adverse events - Safety population

n (%)	Placebo (N=39)	Dupilumab (N=43)
Participants with any TEAE	27 (69.2)	23 (53.5)
Participants with any severe TEAE	1 (2.6)	0
Participants with any treatment emergent SAE	0	1 (2.3)
Participants with any TEAE leading to death	0	0
Participants with any TEAE leading to permanent study intervention discontinuation	0	0
Participants with any treatment emergent AESI	1 (2.6)	0
Participants with any treatment emergent other selected AE	6 (15.4)	11 (25.6)
Participants with any TEAE related to IMP	3 (7.7)	10 (23.3)

TEAE: Treatment emergent adverse event, SAE: Serious adverse event, AESI: Adverse event of special interest
n (%) = number and percentage of participants with at least one TEAE.

Overall, 23 (53.5%) participants in the dupilumab group and 27 (69.2%) participants in the placebo group experienced at least one TEAE. There were no severe TEAEs in the dupilumab group and 1 (2.6%) severe TEAE in the placebo group (PT spinal stenosis). The majority of the TEAEs were assessed as mild or moderate in intensity with similar incidences between mild and moderate in either intervention group. There was 1 (2.3%) participant in the dupilumab group who experienced a treatment-emergent SAE (PT bipolar disorder; assessed as not related to the study intervention by the Investigator). No participants in either intervention group experienced TEAEs leading to death during this study. No participants in either intervention group experienced TEAEs leading to permanent study intervention discontinuation (per the Investigator's judgement) during the study.

No treatment-emergent AESIs were reported in the dupilumab group whereas 1 (2.6%) participant in the placebo group experienced ulcerative keratitis of moderate intensity. The following AESIs or other selected AE groupings were not reported as treatment-emergent event in either intervention group: anaphylactic reaction, symptomatic hypersensitivity, helminthic infection, any severe type of conjunctivitis, any severe type of blepharitis, clinically symptomatic eosinophilia, pregnancy (female participant or male participant partner), significant alanine transaminase (ALT) elevation, symptomatic overdose with investigational medicinal product (IMP) or non-IMP, serious or severe (that last longer than 24 h) injection site reactions, severe or serious infection, potential drug-related hepatic disorder, or malignancy.

The following other selected AE groupings were reported in 11 (25.6%) participants in the dupilumab group and 6 (15.4%) participants in the placebo group:

- Injection site reaction (HLT injection site reaction; nonserious/non severe) with higher incidence in the dupilumab group (11 [25.6%]) versus the placebo group (3 ([7.7%]).
- Conjunctivitis (nonserious/non-severe):
  - Customised MedRA query (CMQ) narrow and FDA AE groupings: 1 (2.3%) participant with conjunctivitis in the dupilumab group and 1 (2.6%) participant with conjunctivitis in the placebo group.
  - CMQ broad AE groupings: 1 additional participant (as compared to narrow and FDA criteria) with blepharitis in the placebo group.

- Keratitis as per CMQ FDA AE groupings in 1 participant in the placebo group (ulcerative keratitis of moderate intensity, also reported as AESI).

The incidence of TEAEs assessed as related to the study intervention by the Investigator was higher in the dupilumab group (10 [23.3%] participants) than in the placebo group (3 [7.7%] participants), most of them being in the injection site reactions HLT (9 [20.9%] participants in the dupilumab group and 2 [5.1%] in the placebo group).

Adolescents

Out of the 8 adolescents (≥12 and <18 years of age, 4 in each intervention group) in this study, 3 TEAEs were reported in 2 participants in the dupilumab group (300 mg q2w regimen; headache in 1 participant and asymptomatic accidental overdose and asymptomatic COVID-19 in 1 participant) and 3 TEAEs were reported in 3 participants in the placebo group (PTs of: suspected COVID-19 in 1 participant, symptomatic COVID-19 in 1 participant, and conjunctivitis bacterial in 1 participant). Per protocol, overdose was defined as at least twice the intended dose during an internal of less than 11 days. None of the TEAEs in the adolescent participants were serious, severe, or led to study intervention discontinuation. All events resolved (with corrective treatment for TEAEs of headache and conjunctivitis) and were assessed as not related to the study intervention by the Investigator.

Table 8 - Overview of adverse event profile: Treatment-emergent adverse events in adolescents - Safety population

n (%)	Placebo (N=4)	Dupilumab (N=4)
Participants with any TEAE	3 (75.0)	2 (50.0)
Participants with any severe TEAE	0	0
Participants with any treatment emergent SAE	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 treatment emergent AESI	0	0
Participants with any treatment emergent other selected AE	1 (25.0)	0
Participants with any TEAE related to IMP	0	0

Immunogenicity

Overall population

Treatment-emergent ADA responses were identified in 4 participants (4 [10.5%] in the dupilumab group [of which 1 participant randomised in the placebo group who incorrectly received dupilumab once, on Day 1] and none in the placebo group); all had low ADA titre (<1000). All 4 (10.5%) ADA positive participants were also NAb positive. There were no treatment boosted ADA responses identified. Dupilumab exposure overlapped between participants with treatment emergent ADA responses and ADA negative participants. There was no observed association between ADA formation and TEAEs or the efficacy of dupilumab in this study.

Adolescents

Adolescent participants in both intervention groups had negative ADA at all time points.

2.3.3. Discussion on clinical aspects

The applicant submitted efficacy and safety data from study EFC16720, a randomised, double-blind, placebo-controlled, multi-centre, parallel-group study to investigate the efficacy and safety of dupilumab over 24 weeks in adult and adolescent participants with chronic inducible cold urticaria who remained symptomatic despite the use of H1-antihistamine treatment. Primary acquired cold urticaria

(ACU) is a type of physical chronic inducible urticaria that is characterized mainly by the appearance of wheals after contact with cold or cooling and rewarming of the skin. As such, the primary objective of the study was to assess the proportion of participants with negative ice cube provocation test compared with placebo. Signs, symptoms and cold urticaria disease activity were further assessed as well as the effect on the participants' quality of life. Study participants were randomised 1:1 and received either weight-tiered dupilumab or placebo during a 24-week treatment period with a later follow-up for 12 weeks.

The study mainly enrolled adult participants (n=74) while a total of 8 adolescent participants were included of whom 4 received dupilumab. This limited number of adolescents overall only allows a descriptive evaluation of efficacy and safety data. A total of 76.8% participants completed the study (treatment and follow-up period) while a substantial number of 23.2% participants discontinued from the study. All adolescent participants completed the study intervention period except 1 participant in the placebo group who discontinued study intervention for lack of efficacy after Week 10 administration. All 82 participants were included in the efficacy and safety analyses.

The study did not meet the primary endpoint and did not demonstrate a statistically significant difference in the proportion of participants with a negative ice cube provocation test. Dupilumab treatment did also not show statistically differences across key secondary and other multiplicity-adjusted secondary endpoints. No difference in efficacy was observed between placebo and dupilumab in the adolescent participants enrolled.

Overall, 53.5% participants in the dupilumab group and 69.2% participants in the placebo group experienced at least one TEAE. There were no severe TEAEs in the dupilumab group and only 1 severe TEAE in one adult placebo patient. The majority of the TEAEs were assessed as mild or moderate in intensity. There was 1 adult participant in the dupilumab group who experienced a treatment-emergent SAE. No participants in either intervention group experienced TEAEs leading to death during this study. No participants in either intervention group experienced TEAEs leading to permanent study intervention discontinuation (per the Investigator's judgement) during the study. No treatment-emergent AESIs were reported in the dupilumab group whereas 1 (2.6%) participant in the placebo group experienced ulcerative keratitis of moderate intensity. The incidence of TEAEs considered to be related to the study intervention by the Investigator was higher in the dupilumab group, mainly driven by injection site reactions HLT. Out of the 8 adolescents, 3 TEAEs were reported in 2 participants in the dupilumab group (1st participant: headache; 2nd participant: asymptomatic accidental overdose and asymptomatic COVID-19) and 3 TEAEs were reported in 3 participants in the placebo group (1st: suspected COVID-19; 2nd: symptomatic COVID-19; 3rd: conjunctivitis bacterial). None of the TEAEs in the adolescent participants were serious, severe, or led to study intervention discontinuation. All events resolved (with corrective treatment for TEAEs of headache and conjunctivitis) and were assessed as not related to the study intervention by the Investigator. In the overall safety population, ADA-formation after dupilumab treatment was observed with a low incidence. Adolescent participants in both intervention groups had negative ADA at all time points.

The safety results obtained in study EFC16720 for adults and adolescents are consistent with the known safety profile of dupilumab. Overall, no new safety findings were identified in this study. No amendments of the product information were introduced by the applicant which is supported.

3. CHMP’s overall conclusion and recommendation

The applicant submitted efficacy and safety data from study EFC16720, a phase 3 clinical study designed and conducted to investigate the efficacy and safety profile of dupilumab in adult and adolescent participants with chronic inducible cold urticaria who remain symptomatic despite the use of H1-antihistamine treatment. A total of 8 adolescents were enrolled beside 74 adult participants. The study did not meet the primary endpoint and was not able to demonstrate beneficial effects of dupilumab in reducing reaction to cold and improving cold induced signs, symptoms and quality of life across adults and adolescents. The collected safety data in adult and adolescent participants are consistent with the known safety profile of dupilumab. It is agreed with the MAH that no amendment of the product information is warranted.

☒ Fulfilled:

No regulatory action required.

4. Request for supplementary information

None