AMENDED CLINICAL TRIAL PROTOCOL 01

Protocol title:	**A randomized, double-blind, placebo-controlled, multi-center, parallel-group study of dupilumab in patients with chronic inducible cold urticaria who remain symptomatic despite the use of H1-antihistamine treatment**
Protocol number:	**EFC16720**
Amendment number:	**01**
Compound number (INN/Trademark):	**SAR231893/REGN668** **dupilumab/Dupixent®**
Study phase:	**Phase 3**
Short title:	**Dupilumab for the treatment of chronic inducible cold urticaria in patients who remain symptomatic despite the use of H1-antihistamine** **LIBERTY-CINDU CUrIADS**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
Legal registered address:	**1 avenue Pierre Brossolette** **91385 Chilly-Mazarin Cedex** **FRANCE**
Monitoring Team's Representative Name and Contact Information	

Regulatory agency identifier number(s):

IND:	IND105379
EudraCT:	2020-003756-33
NCT:	NCT04681729
WHO:	U1111-1246-6913
Other:	Not applicable

Date:	27-Sep-2022	Total number of pages: 137

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/ countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 01	All	27 September 2022, version 1 (electronic 1.0)
Original Protocol		25 September 2020, version 1 (electronic 2.0)

Amended protocol 01 (27 September 2022)

This amended protocol (amendment 01) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The primary purpose of this amendment is to redefine the Cold Urticaria Activity Score (ColdUAS) efficacy endpoints. It is anticipated that the newly defined ColdUAS endpoints are more sensitive to detect a treatment effect and will better address the objectives of the EFC16720 study.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis - Objectives and endpoints/ Section 3 Objectives and endpoints/ Section 9.4.1 efficacy analyses/ Section 10.13 Appendix 13 - Estimands for main endpoints	The following ColdUAS secondary endpoints have been removed: - Proportion of participants with cold exposure triggered urticaria signs and symptoms at Week 12 and Week 24 as measured by ColdUAS compared with placebo - Proportion of days with cold exposure triggered urticaria signs and symptoms at Week 12 and Week 24 as measured by ColdUAS compared with placebo - Proportion of participants with severe cold exposure triggered urticaria signs and symptoms at Week 12 and Week 24 as measured by ColdUAS compared with placebo - Proportion of days with severe cold exposure triggered urticaria signs and symptoms at Week 12 and Week 24 as measured by ColdUAS compared with placebo	Newly proposed secondary endpoints are considered sensitive to detect a shift in cold urticaria signs and symptoms severity, either via reduction in signs/symptoms severity score or change in proportion of symptom free days. Symptom free days are considered clinically meaningful for assessment of treatment benefit. [redacted] Of note, there will be no change in data collection for ColdUAS. The proposed modifications affect the ColdUAS data analysis.

Section # and Name	Description of Change	Brief Rationale
	And replaced by the following secondary endpoints: • 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 And the following tertiary/exploratory endpoint: • [redacted]	
Section 1.1 Synopsis Objectives and endpoints/ Section 3 Objectives and endpoints/ Section 9.4.1 efficacy analyses	The following endpoints were no longer considered as secondary endpoints but were moved to exploratory endpoints: • Patient Global Impression of Change (PGIC) of primary acquired chronic inducible ColdU at Week 12 and Week 24 compared with placebo • Change from baseline in Patient Global Impression of Severity (PGIS) of primary acquired chronic inducible ColdU at Week 12 and Week 24 compared with placebo	PGIS and PGIC scales are used in the study as a benchmark/anchor instrument for the analysis of the other patient-reported outcomes (PROs). Therefore, they were considered exploratory endpoints rather than secondary ones.
Section 1.1 Synopsis Objectives and endpoints/ Section 3 Objectives and endpoints/ Section 9.4.1 efficacy analyses/ Section 10.13 Appendix 13 - Estimands for main endpoints	The following secondary endpoint was removed: • Time to first rescue therapy for primary acquired chronic induced ColdU during the planned treatment period compared with placebo	Cold urticaria signs and symptoms as well as need for rescue therapy occur episodically. Analysis of "Time to onset of rescue therapy" will likely be confounded by this factor. This endpoint was removed since the Sponsor considered the secondary endpoint of "proportion of participants receiving rescue therapy" already defined in the protocol as sufficient to evaluate the effect of the study intervention on rescue therapy need.
Section 3 Objectives and endpoints/ Section 9.4.1 efficacy analyses	The following tertiary/exploratory endpoints were removed: • Change from baseline in [redacted] at Week 12 and at Week 24 compared with placebo • Change from baseline in [redacted] over time up to Week 24 compared to placebo • Change from baseline in HRQoL as measured by Cold Urticaria Quality of Life (ColdU-QoL) questionnaire at Week 24 compared placebo	[redacted] scoring is not validated by the scale developer and therefore the endpoints evaluating change in [redacted] score were removed. This endpoint was removed from tertiary endpoints as it was already mentioned as a secondary endpoint (was duplicated by error).

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Analysis of secondary endpoints/ Section 9.4.1 Efficacy analyses/ Section 10.13 Appendix 13 - Estimands for main endpoints	• Change in the imputation rule from "worst possible value" to "worst observation carried forward (WOCF) approach" for participants taking highly influential prohibited medications and/or highly influential rescue medications. • The following changes related to missing data handling were made: For participants who discontinue study intervention due to lack of efficacy, all data collected after discontinuation will be used in the analysis, and a WOCF approach will be used to impute missing Week 24 value if needed. For participants who discontinue study intervention not due to lack of efficacy, a multiple imputation approach will be used to impute missing Week 24 value, and this multiple imputation will use all participants excluding participants who have taken the highly influential prohibited medications and/or highly influential rescue medications on or before Week 24 and excluding patients who discontinue due to lack of efficacy on or before Week 24.	Handling of missing data after taking highly influential prohibited medications and/or highly influential rescue medications or after withdrawal of study intervention are modified to include each participant's own worst data in order to better reflect the clinical scenario of treatment failure.
Section 6.3 Measures to minimize bias: Randomization and blinding	• Code breaking: Investigator could decide at his/her discretion to contact the Sponsor to discuss the situation prior to unblinding participant's intervention assignment.	To clarify that the responsibility to unblind treatment assignment in emergency situations resides solely with the investigator as per the EMA GCP Inspectors Working Group (GCP IWG) and the Clinical Trial Facilitation Group (CTFG). Consequently, the Sponsor cannot require or insist on being involved in the decision to unblind, stall or delay in any way the unblinding of trial participant treatment in emergency situations.
Section 8.1.5 Cold Urticaria Activity Score	• The following text was removed: "[redacted]. The [redacted] will be assessed over prior to baseline, Week 12, and Week 24". • Text was corrected as follows: After each week of completion, participants will be asked 2 additional questions about the overall disease activity of their ColdU in the past week using a 4-point Likert scale from "No disease activity" to "High disease activity" and 1 question about their current disease activity in the past week compared with before treatment using a 4-point Likert scale. And the following text was deleted : "After each 2 weeks of completion, participants will be asked about the overall disease activity of their ColdU in the past 2 weeks using a 4-point Likert scale from "No disease activity" to "High disease activity", and they should rate disease activity in the second	[redacted] scoring is not validated by the scale developer and therefore the endpoints evaluating change in [redacted] score were removed. Correction of error

Section # and Name	Description of Change	Brief Rationale
	week compared with first week from “markedly higher than in the first week” to “markedly lower than in the first week”.	
Section 10.1.6 Dissemination of clinical study data	• Reference to ‘clinicalstudydatarequest.com’ was changed to “https://vivli.org”	Change in the Sponsor’s data sharing platform.
10.15 Appendix 15: Protocol amendment history	• Section updated to state that the Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.	Aligned with Sanofi procedures.
Global	• Minor editorial/formatting changes.	Correction of minor editorial/formatting issues

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

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

Short title: Dupilumab for the treatment of chronic inducible cold urticaria in patients who remain symptomatic despite the use of H1-antihistamine

Rationale:

Chronic inducible urticaria (CIndU) is a subtype of chronic urticaria characterized by recurrent itchy wheals, angioedema, or both with a minimum disease duration of 6 weeks, that only occurs after exposure to defined external triggers and is classified according to the stimulus that provokes the development of signs and symptoms (1, 2). Unlike chronic spontaneous urticaria (CSU), symptoms in CIndU patients (itchy wheals and angioedema) develop only and reproducibly in response to the trigger stimulus that is specific for their condition (eg, cold exposure in cold urticaria [ColdU]). The triggers that lead to the urticarial signs and symptoms in CIndU patients are mainly physical or chemical stimuli, which results in 2 main sub-groups of CIndU: physical and non-physical, respectively. Physical triggers include pressure (in delayed pressure urticaria [DPU]), radiation (in solar urticaria), friction (in symptomatic dermographism), temperature (in cold and heat urticaria), and vibration (in vibratory angioedema). Chemical triggers of CIndU reactions include water (in aquagenic urticaria), sweat (in cholinergic urticaria [CholU]), and other urticariogenic chemical compounds (in contact urticaria) (3).

Chronic inducible urticaria has an estimated prevalence of about 0.5% in the general population (4), and has substantial impact on quality of life (QoL) in many patients, mainly due to the need for trigger avoidance. Within the group of CIndU, most CIndU subtypes are rare and therefore very difficult to study (1). The most common are symptomatic dermographism, CholU and ColdU (also called chronic inducible cold urticaria), chronic inducible ColdU being the second most common form of physical urticaria (1). Cold urticaria is a relatively rare disorder with a reported prevalence of 0.05% as per one study in Europe (4), with a higher prevalence in northern climates. It is also self-limited, lasting 4 to 5 years on average (5).

Chronic inducible ColdU manifests as wheals, angioedema, or both secondary to the release of mast cell mediators after exposure to cold or cooling and rewarming of the skin. The clinical symptoms occur within minutes after skin contact with cold air, cold liquids, cold solid objects, or evaporation-based cooling and persist in general for a few hours (4). In severe cases, patients can develop systemic involvement including anaphylaxis. Local angioedema affecting the lips, tongue, or pharyngeal tract has been associated with the ingestion of cold beverages or food, and shock like reactions are reported after swimming in cold water. Cold urticarias can be classified as those with typical responses to cold provocation tests, those with atypical responses to cold provocation, and those with familial forms. Primary acquired chronic inducible ColdU is the most common form of chronic inducible ColdU and is considered idiopathic in nature. Historically the

majority (96%) of patients with acquired cold-induced urticaria have been shown to have primary cold-induced urticaria, with only rare occurrences of secondary cold-induced urticaria (6). Secondary acquired chronic inducible ColdU is very rare and associated with an underlying disease most commonly cryoglobulinemia, but infectious causes, leukocytoclastic vasculitis, and some drug-induced cases have been reported. Both primary and secondary acquired chronic inducible ColdU have typical positive responses to cold provocation. Several other rare forms of atypical acquired chronic inducible ColdU exist, which have negative immediate tests to cold provocation and include systemic atypical acquired chronic inducible ColdU, cold-dependent dermographism, cold-induced CholU, delayed chronic inducible ColdU, and localized cold-reflex urticaria. Lastly, hereditary forms of chronic inducible ColdU have been described: 1) Familial cold autoinflammatory syndrome caused by mutations in NLRP3 (cryopyrin) and is inherited in an autosomal dominant manner, which includes cryopyrin-associated periodic syndromes, Muckle-Wells syndrome and neonatal-onset multisystem inflammatory disease; 2) Familial atypical cold urticaria inherited in an autosomal dominant fashion with having phospholipase C-g2-associated deficiency and immune dysregulation (PLAID) (4).

Chronic inducible urticarias are diagnosed based on the patient history and the results of provocation testing (1, 2). The treatment of inducible urticaria is trigger avoidance and prophylaxis by H1-antihistamines that prevent the effects of the mast cell-mediator histamine (4, 7) or, if antihistamines are not effective, agents that prevent the activation of mast cells (eg, anti-immunoglobulin E [IgE] omalizumab) (7, 8, 9). The consensus recommendations for CIndU management (EAACI/GA²LEN/EDF/UNEV) (1) are mainly based on treatments approved for CSU, and some clinical data available in patients suffering from various types of CIndUs (cholinergic, symptomatic dermographism, ColdU). The recommended therapies are, in general, not approved for CIndU by regulatory agencies, with only limited specific countries where antihistamines are approved under broader “urticaria” indications. All patients are advised to avoid prolonged skin contact with cold objects or exposure to cold air temperatures. The first-line symptomatic therapy for CIndU is a non-sedating second-generation H1 antihistamine at approved doses for CSU. In patients who do not obtain complete control, increasing the dose up to 4 times approved doses for CSU is recommended. Steps 3 and 4of treatment options include omalizumab and ciclosporin A, respectively. All these treatments are used off label and lack good evidence of effectiveness in patients with CIndU.

Chronic inducible urticarias last several years and often pose a great treatment challenge because of their resistance to first-line therapy with H1-antihistamine (1). They are debilitating, often causes systemic reactions including anaphylaxis in severe cases and severely affect patient QoL (7, 8). Avoidance of offending triggers poses massive changes to everyday life and therefore is typically not feasible. Thus, the need for approved treatment options for CIndU, especially for chronic inducible ColdU that have proven to be safe and efficacious in chronic inducible ColdU patients, is high.

Chronic inducible ColdU presents as pruritic wheals with or without angioedema secondary to the release of mediators from mast cells after exposure of the skin to cold air, liquid, or cold objects. Degranulation of mast cells in CIndU is held to be mediated by Fc epsilon receptor (FcεRI) activation, through cell surface-bound IgE cross-linked by as of yet unidentified autoallergens. The subsequent release of histamine and other pro-inflammatory mediators leads to local tissue edema and pruritus. Many symptoms of urticaria are mediated primarily by the actions of

histamine (a mast cell mediator) on the H1-receptors, and treatment with H1-antihistamine is a mainstay of therapy (1). Approximately 50% of patients achieve symptomatic control with conventional H1-antihistamine therapy (2). Increasing the dose of anti-histamines in some cases has been demonstrated to be effective but not in all cases (10). Omalizumab anti-IgE which is approved for CSU may be efficacious in ColdU, however it is not approved for use in this specific condition. The mechanism by which omalizumab exerts its therapeutic effects is likely constrained to reduction in serum IgE and consequent down regulation of high affinity IgE receptors. Novel therapies that target signaling pathways important for mast cell survival and function may provide additional treatment options for patients with this disease who are not responsive to treatment with H1-antihistamine therapy. Interleukin-4 (IL-4)/IL-13 signaling is required for antibody isotype switching to IgE production in B cells and contribute to mast cell survival and function (4, 7). Therefore, blockade of IL-4/IL-13 by dupilumab represents a novel therapeutic approach for chronic inducible ColdU patients.

Dupilumab is a human monoclonal antibody (mAb) directed against the interleukin-4 receptor alpha subunit (IL-4Rα), which is a component of IL-4 receptors Type I and Type II, the latter being also a receptor for IL-13. The binding of dupilumab to IL-4Rα results in blockade of both IL-4 and IL-13 signaling. As a targeted immunomodulatory agent, dupilumab selectively inhibits the type 2 immune response, which is responsible for several pathophysiological mechanisms including mast cell and basophil degranulation. Dupilumab has shown efficacy in multiple diseases with underlying type 2 inflammation such as atopic dermatitis (AD), asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), and eosinophilic esophagitis (EoE). In these clinical studies, treatment with dupilumab resulted in continuous decreases in blood total IgE. Moreover, in CRSwNP studies, a decrease in urinary leukotriene E4 (LTE4) and prostaglandin D2 metabolite (PGDM) suggests that dupilumab has impact on mast cell function. In a proof of concept study in EoE dupilumab modulated type 2 inflammatory genes including genes associated with mast cell activation (11).

In a small case series of patients who had concurrent AD and CSU (12) and were resistant to omalizumab, treatment with dupilumab improved their urticaria. The same has been observed in 1 patient with chronic inducible ColdU (13). These data further support the rationale to target IL-4/IL-13 signaling with dupilumab in patients with chronic urticaria. As this is a novel therapy that acts further upstream than IgE-targeted therapies, the clinical study proposed here will test the efficacy of dupilumab in patients who have failed antihistamines alone.

Based on available literature data for ColdU and dupilumab mechanism of action, the present study will be evaluating the efficacy and safety of dupilumab in patients with primary acquired chronic inducible ColdU.

Objectives and endpoints

Table 1 – Objectives and endpoints

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 hive/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 induced 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

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

Overall design:

The EFC16720 study is a 24-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center study to evaluate the use of dupilumab in adults and adolescents (≥12 to <18 years old) with primary acquired chronic inducible ColdU who remain symptomatic despite the use of H1-antihistamine. Participants using H1-antihistamine regularly/daily or as needed are eligible since both treatment regimens are common in patients with ColdU (5). The study is designed to test the hypothesis that dupilumab will increase the proportion of participants with negative ice cube provocation test compared with placebo. Negative ice cube provocation test is defined as absence of a confluent hive/wheal at the entire skin site of exposure after ice cube provocation test.

Chronic inducible ColdU signs and symptoms will be evaluated after a provocation test by the Investigator (hives/wheals intensity) and participant (itch severity, skin pain, skin burning sensation). In addition, chronic inducible ColdU disease activity will be assessed daily by the participant using the Cold Urticaria Activity Score (ColdUAS) questionnaire in an e-diary where the participant will report his/her skin reactions (wheals and swelling), skin sensations (itching, burning, pain or feeling hot), if they have been in contact with cold temperatures that usually cause skin reactions, if they have avoided trigger exposure, and overall symptoms severity. The study will also assess the effect of dupilumab on urticaria control, participants´ health-related quality of life (HRQoL) and overall health status, proportion of patients with cold urticaria requiring emergency medical care visit or treatment with epinephrine and on reduction of rescue therapy.

Disclosure Statement:
This is a parallel, treatment study with 2 arms that is blinded/masked for participants and Investigators.

Number of participants:

The total anticipated number of participants randomized in the study is 78. This corresponds to approximately 39 participants who will be randomly assigned to each intervention arm: the dupilumab or the placebo treatment arm. At least 4 participants randomized in the study will be adolescents (≥12 to <18 years old) who will be recruited in a few selected countries. Randomization will be stratified by age (adolescent versus adult) and within adult group by country and background H1-antihistamine regular/daily use (Yes/No) (see Section 6.1.2 for additional background therapy details).

Number of participants using H1-antihistamine as needed prior to study entry should be at least [redacted].

Intervention groups and duration:

Participants who satisfy the inclusion and exclusion criteria will be randomized (1:1) to 1 of the following investigational medicinal product (IMP) treatment groups:

- Dupilumab: 300 mg every 2 weeks (q2w) for adults; 200 mg q2w for adolescents ≥30 kg and <60 kg at baseline or 300 mg q2w for adolescents ≥60 kg at baseline.
- Matched placebo.

Duration of study period (per participant)

- Screening period (2 to 4 weeks).
- Randomized IMP treatment period (24 weeks).
- Post IMP treatment period (12 weeks).

Study interventions

Investigational medicinal product:

- Dupilumab 300 mg and placebo matching dupilumab 300 mg supplied in prefilled syringes that are visually indistinguishable.
- Dupilumab 200 mg and placebo matching dupilumab 200 mg supplied in prefilled syringes that are visually indistinguishable.

Dupilumab

Formulation:

- Dupilumab 300 mg: a 150 mg/mL dupilumab solution in a pre-filled syringe to deliver 300 mg in a 2 mL injection.
- Dupilumab 200 mg: a 175 mg/mL dupilumab solution in a pre-filled syringe to deliver 200 mg in a 1.14 mL injection.

Route of administration: Subcutaneous (SC) injection.

Dose regimen:

- One injection of 300 mg q2w after an initial loading dose of 600 mg (2 injections of 300 mg) on Day 1 for all adult participants and for adolescents weighing ≥60 kg.
- One injection of 200 mg q2w after an initial loading dose of 400 mg (2 injections of 200 mg) in adolescent participants ≥30 kg and <60 kg.

Placebo

Formulation:

- Placebo matching dupilumab 300 mg: identical formulation to the active 300 mg formulation without dupilumab, in a pre-filled syringe to deliver placebo in a 2 mL injection or,
- Placebo matching dupilumab 200 mg: identical formulation to the active 200 mg formulation without dupilumab, in a pre-filled syringe to deliver placebo in a 1.14 mL injection.

Route of administration: SC injection.

Dose regimen:

- One injection of placebo matching 300 mg q2w after an initial matching placebo loading dose of 600 mg (2 injections of placebo matching 300 mg) on Day 1 for all adult participants and for adolescents weighing ≥60 kg.
- One injection of placebo matching 200 mg q2w after an initial matching placebo loading dose of 400 mg (2 injections of placebo matching 200 mg) in adolescent participants ≥30 kg and <60 kg.

Noninvestigational medicinal products

During the study, participants should continue their established standard of care background therapy with a long-acting non-sedating H1-antihistamine, at up to 4-fold the approved dose for CSU.

- Participants who used H1-antihistamine regularly/daily prior to study entry should continue to take it daily. Note: regular/daily use of H1-antihistamine prior to study entry is

defined as H1-antihistamine intake for at least 4 days per week for at least 1 month prior to screening visit (Visit 1)

- Participants who took H1-antihistamine as needed prior to study entry should limit the use to short-term.

The H1-antihistamine dose used during the study should be the same dose the participants took to prevent ColdU symptoms prior to study entry ("prescreening dose"). However, if participants experience a flare rescue therapy may be initiated. Please refer to Section 6.5.1 for rescue therapy.

If participants are on a dose higher than 4-fold the approved CSU dose at the screening visit (Visit 1), the Investigator can adjust the participant's dose within the stipulated range at the screening visit (Visit 1).

The following list of H1-antihistamines is allowed as background and rescue therapy during the study (see Section 6.1.2 and Section 6.5.1), and noted with their recommended dose:

- Cetirizine 10 mg once per day (qd).
- Levocetirizine dihydrochloride 5 mg qd
- Ebastine 10 mg qd
- Fexofenadine 60 mg twice per day or 180 mg qd
- Loratadine 10 mg qd
- Desloratadine 5 mg qd
- Bilastine 20 mg qd
- Rupatadine 10 mg qd
- Other H1-antihistamines after discussion with the Sponsor

For other information related to H1-antihistamine including safety precautions, please refer to the locally approved product labeling.

Background therapy will be supplied by Sponsor's local affiliate as locally required or by sites. Reimbursement will be provided when deemed necessary and as per country regulation.

Post-study access to IMP

The Sponsor does not plan to provide post-study access to the IMP.

Statistical considerations:

- **Sample size calculations**

  Sample size is calculated based on the following assumptions:

1. The placebo group has [redacted] participants with negative ice cube provocation test at Week 24 and the dupilumab group has [redacted] 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 randomized to the dupilumab group and the placebo group.

With these assumptions, 39 participants per group (78 participants in total) will provide 90% power to detect the difference of [redacted] response rate in the dupilumab group and [redacted] response rate in the placebo group. The sample size calculations were performed using nQuery+nTerim 4.0.

- **Randomization**

Participants will be randomized in a 1:1 ratio to dupilumab or placebo. The randomization will be first stratified by age (adults versus adolescents) with at least 4 adolescents. Then in adult's randomization will be stratified further by country and background H1-antihistamine regular/daily use (Yes/No). Randomization will not be stratified further in adolescents.

Number of participants using H1-antihistamine as needed prior to study entry should be at least [redacted].

- **Analysis population**

The primary analysis population for the efficacy endpoints will be the randomized intent-to-treat population which includes all participants who have been allocated to a randomized treatment regardless of whether the treatment kit was used or not. The efficacy analyses will be conducted according to the treatment to which they were randomized.

The analysis population for safety endpoints is defined as all randomized participants exposed to study medication, regardless of the amount of treatment administered. The safety analyses will be conducted according to the treatment participants actually received.

- **Primary analysis**

The primary efficacy endpoint is the proportion of participants with negative ice cube provocation test at Week 24. The statistical hypothesis for comparing dupilumab against placebo on the primary endpoint is:

- Null hypothesis H0: No treatment difference between dupilumab and placebo.
- Alternative hypothesis H1: There is a treatment difference between dupilumab and placebo.

The primary efficacy endpoint will be analyzed using the Cochran-Mantel-Haenszel test stratified by region 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 will be derived, and the corresponding odd ratios and the 95% confidence interval (CI) will be reported. Participants who receive highly influential prohibited medications and/or highly influential rescue medications (details of selection will be specified in the statistical analysis plan [SAP]) will be considered as having positive ice cube provocation tests for time points after the

medication usage. For other participants, all available data including those collected during the off-treatment period will be used to determine the positive/negative ice cube provocation test outcomes. Participants with missing ice cube provocation test data at Week 24 will be considered as having positive ice cube provocation tests.

- **Analysis of secondary endpoints**

  The continuous secondary endpoints at Week 24 will be analyzed using Analysis of covariance (ANCOVA) with multiple imputation. For participants taking highly influential prohibited medications and/or highly influential rescue medications (details of selection will be specified in the SAP), their data after the medication usage will be set to missing, and the WOCF approach (worst postbaseline observation for the participant will be carried forward) will be used to impute missing Week 24 value (for participants whose postbaseline values are all missing, the participant's baseline value will be used to impute the missing endpoint value). Participants who discontinue the treatment prematurely are encouraged to follow the planned clinical visits. For participants who did not take the highly influential prohibited medications and/or highly influential rescue medications, all data collected after treatment discontinuation will be used in the analysis. For these participants, missing data may still happen despite all efforts have been tried to collect the data after treatment discontinuation. For participants who discontinue study intervention due to lack of efficacy, all data collected after discontinuation will be used in the analysis, and a WOCF approach will be used to impute missing Week 24 value if needed. For participants who discontinue study intervention not due to lack of efficacy, a multiple imputation approach will be used to impute missing Week 24 value, and this multiple imputation will use all participants excluding participants who have taken the highly influential prohibited medications and/or highly influential rescue medications on or before Week 24 and excluding patients who discontinue due to lack of efficacy on or before Week 24. Each of the imputed complete data will be analyzed by fitting an analysis of covariance model with the baseline value of the endpoint, treatment group, region (combined countries), and background H1-antihistamine regular/daily use (Yes/No) as covariates. Statistical inference obtained from all imputed data will be combined using Rubin's rule. Descriptive statistics including number of participants, mean, standard error, and least squares (LS) mean changes (and standard error) score will be provided. In addition, difference of the dupilumab group against placebo in LS means and the corresponding 95% CI will be provided along with the p-values.

  The continuous endpoints at Week 12 will be analyzed in a similar way as the secondary endpoints at Week 24.

  The binary endpoints will be analyzed in the similar way to the primary efficacy endpoint.

  The safety variables, including adverse events (AEs), laboratory parameters, vital signs, electrocardiogram (ECG), and physical examinations will be summarized using descriptive statistics.

- **Missing data handling**

  For continuous endpoints, missing data due to lack of efficacy will be imputed using WOCF approach and missing data not due to lack of efficacy will be imputed using a multiple imputation method, which will use all participants except those who have taken the highly influential prohibited medications and/or highly influential rescue medications and excluding patients who discontinue due to lack of efficacy. For binary endpoints, missing data will be considered as non-responder.

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

- **Multiplicity considerations**

  A multiplicity hierarchical testing will be proposed to control the overall Type-I error rate for testing the primary endpoint, selected patient-reported outcome (s) (PRO) and the other key secondary endpoints. The study is considered positive when the primary endpoint achieves statistical significance. Detailed multiplicity adjustment procedure for the efficacy endpoints will be described in the study SAP.

- **Planned database lock date**

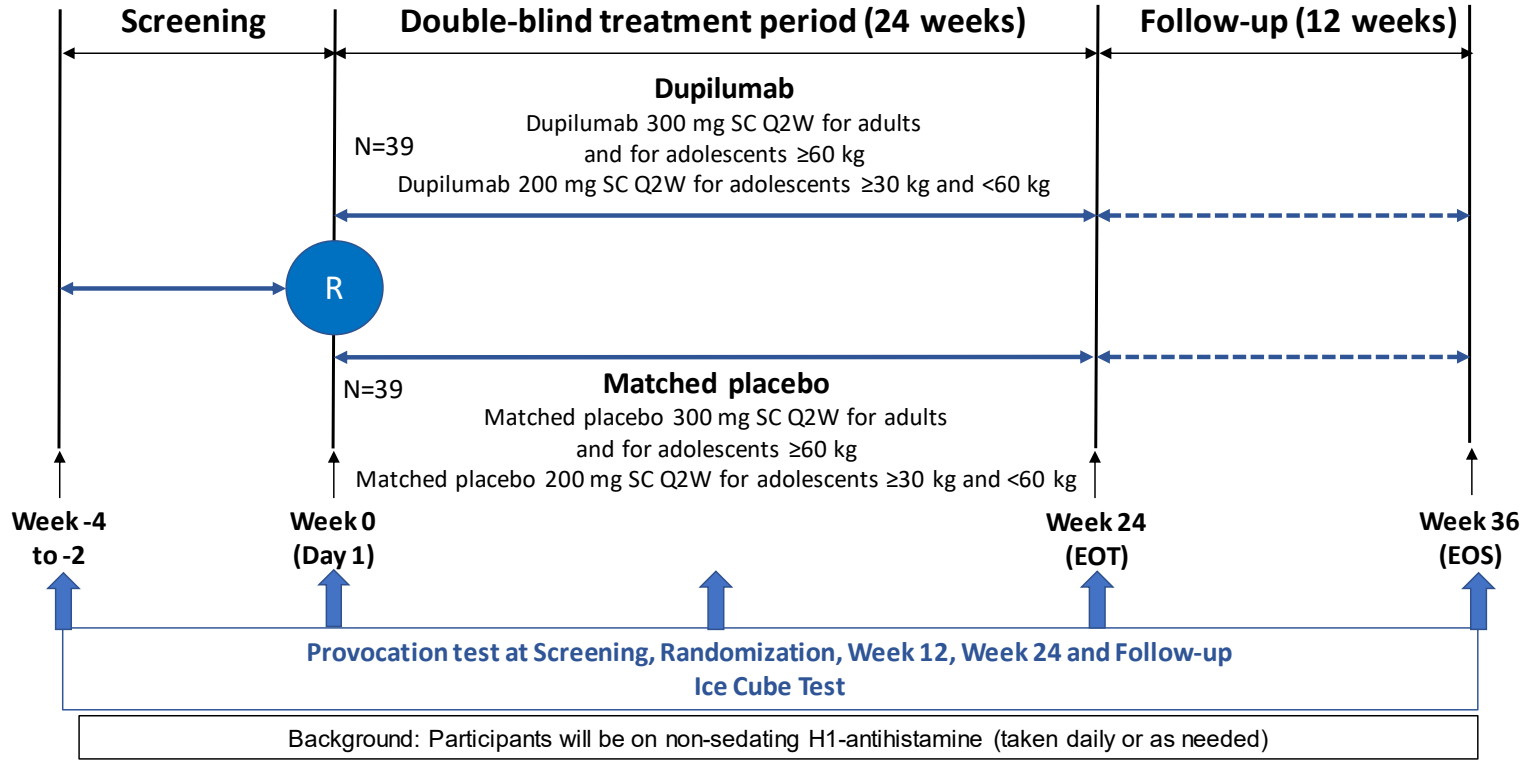
  A primary database lock will be performed when all randomized participants have completed their treatment phase. Final analyses in the clinical study report (CSR) will be based on all data collected up to this database lock.

  The database will be updated at the end of the study for all participants to include the post-treatment follow-up information and updates for the events previously ongoing at the time of the primary lock. Additional data between this database lock and last participant completing last visit will be summarized in a CSR addendum.

Data Monitoring Committee: No

1.2 SCHEMA

Figure 1 - Graphical study design



Dupilumab 300 mg Q2W, administered as 1 SC injection of dupilumab 300 mg (2 mL)
Dupilumab 200 mg Q2W, adminstered as 1 SC injection of dupilumab 200 mg (1.14 mL)
Matched placebo is prepared in the same formulation without the addition of protein (ie, the active substance)
A loading dose equivalent to treatment group assigned will be administered on Day 1

Abbreviations: EOS: End of study; EOT: End of treatment; Q2W: Every 2 weeks; N: number of participants; R: Randomization; SC: Subcutaneous

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening (2 to 4 weeks before Day 1)	Intervention period (Weeks)			Follow-up (12 weeks)
		0 (Day 1)	12 ±3 days	24 ±3 days	36 ±7 days
Visit	**1**	**2[a]**	**3**	**4 (EOT)**	**5 (EOS)**
Screening/baseline:					
Informed consent	X				
Medical history including systemic hypersensitivity reactions and ACUSI[b]	X				
Prior and concomitant medication[c]	X	X	X	X	X
Demographics	X				
Inclusion/exclusion criteria	X	X			
Patient e-diary training	X				
Randomization		X			
Study intervention					
Call IVRS/IWRS	X	X	X	X	X
IMP administration		←----------X[d]----------→			
Dispense/Upload electronic diary[e]	X	←----------X----------→			X
Dispense EpiPen[f]		X			
Safety[g]					
Physical examination[h]	X	X		X	X
Vital signs[i]	X	X	X	X	X
Electrocardiogram (12 lead)[j]	X				

Procedures	Screening (2 to 4 weeks before Day 1)	Intervention period (Weeks)			Follow-up (12 weeks)
		0 (Day 1)	12 ±3 days	24 ±3 days	36 ±7 days
Visit	**1**	**2[a]**	**3**	**4 (EOT)**	**5 (EOS)**
Hematology, biochemistry, urine analysis[k]	X	X	X	X	X
Hepatitis, HIV Serology, TB test[l]	X				
Pregnancy test[m]	Serum	Ur	Ur	Ur	Ur
AE reporting, including SAEs	X	X	X	X	X
Pharmacokinetics and ADA[g]					
Serum PK samples for dupilumab concentration[n]		X	X	X	X
Anti-dupilumab antibody[n]		X	X	X	X
Biomarkers[g]					
Serum total IgE		X	X	X	X
Basophil activation test at selected sites (optional) [o]		X	X	X	
Archive serum and plasma samples (optional)[p]		X	X	X	X
DNA (whole blood) samples - Optional[q]		X			
RNA (whole blood) samples - Optional[r]		X		X	

Procedures	Screening (2 to 4 weeks before Day 1)	Intervention period (Weeks)			Follow-up (12 weeks)
		0 (Day 1)	12 ±3 days	24 ±3 days	36 ±7 days
Visit	**1**	**2[a]**	**3**	**4 (EOT)**	**5 (EOS)**
Efficacy [g]					
Ice cube provocation test[s]	X	X	X	X	X
Wheal intensity Likert scale after provocation test[t]		X	X	X	X
Peak pruritus NRS, peak pain NRS, and peak burning sensation NRS after provocation test		X	X	X	X
ColdUAS	X	X	X	X	
UCT	X	X	X	X	X
DLQI/CDLQI[u]		X		X	
ColdU-QoL		X		X	
PGIC			X	X	
PGIS	X	X	X	X	
EQ-5D-5L		X		X	
Healthcare resource utilization/productivity (missed school/workdays)[v]		X		X	

Abbreviations: ACUSI = Acquired Cold Urticaria Severity Index; ADA = antidrug antibodies; AE = adverse event; AESI = adverse event of special interest; CDLQI = Children's Dermatology Life Quality Index; ColdUAS= Cold Urticaria Activity Score; ColdU-QoL = Cold Urticaria Quality of Life; DLQI = dermatology life quality index; DNA = deoxyribonucleic acid; ECG = electrocardiogram; eCRF = electronic case report form; e-diary = electronic diary, EOS = End of study; EOT= End of treatment; EQ-5D-5L = 5-level EuroQol 5-dimensional questionnaire; HBc Ab = hepatitis B core antibody; HBs Ab = hepatitis B surface antibody; HBs Ag = hepatitis B surface antigen; HBV = hepatitis B virus; HCRU = Healthcare resource utilization; HCV = hepatitis C virus; HCV Ab = hepatitis C virus antibodies; HIV = Human Immunodeficiency Virus; IgE = immunoglobulin E; IMP = investigational medicinal product; IVRS = interactive voice response system; IWRS = interactive web response system; NRS, Numerical Rating Scale; OCS = oral corticosteroids; PGIC = patient global impression of change; PGIS = patient global impression of severity; PK = pharmacokinetic; q2w = every 2 weeks; RNA= ribonucleic acid; SAE = serious adverse event; SC = subcutaneous; TB = tuberculosis; UCT = urticaria control test; Ur = urine.

a Randomization/baseline Visit is defined as Day 1. All assessments at Visit 2 (Day 1) are to be conducted pre-IMP dose with the exception of the assessment of local tolerability of SC injections.

b ACUSI will be captured in the eCRF.

c Concomitant medication, including rescue OCS taken since last visit will be collected throughout the study.

d Loading dose at Day 1 (Visit 2): 600 mg/matched placebo (2 SC injections) for 300 mg/matched placebo q2w regimen for adults and adolescents ≥60 kg OR 400 mg/matched placebo (2 SC injections) for 200 mg/matched placebo q2w regimen for adolescents ≥30 kg and <60 kg. Investigational medicinal product will be administered every other week. The planned last dose is at Week 22. Participants are allowed to self-inject IMP at home after appropriate training of the participants (or parent/legally authorized representatives, or caregivers).

e Electronic diary is used for daily recording of ColdUAS and antihistamine medication from screening up to Week 24. This device is dispensed at screening visit (Visit 1), including instructions for use. At the EOT, the e-diary is returned to the study center. For UCT, DLQI (≥16 years old)/CDLQI (<16 years old), ColdQoL and EQ-5D-5L the participant will fill in the questionnaires during their study center visit in the e-diary. The e-diary will be also used to complete peak pruritus NRS, peak pain NRS, and peak burning sensation NRS, after the provocation test. Participants will complete the PGIS and PGIC on the e-diary after they have answered the peak pruritus NRS, peak pain NRS and peak burning sensation NRS.

f EpiPen or equivalent to be provided locally.

g Assessments/procedures should be conducted in the following order: patient-reported outcomes questionnaires, safety and laboratory assessments (including sample collection for ADA, PK, biomarker, and optional DNA and RNA), ice cube provocation test, participant´s and Investigator's assessment of signs and symptoms after provocation test, and administration of IMP.

h Physical examinations will include skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems.

i Vital signs, including systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), body temperature (°C), and respiratory rate will be measured at every visit prior and after provocation test. Height (cm) will be measured at screening visit (Visit 1) only. Body weight (kg) will be measured at screening visit (Visit 1) and at EOT/EOS Visits.

j ECG to be locally collected and read.

k Hematology will include hemoglobin, hematocrit, platelet count, total white blood cell count, differential count, and total red blood cell count. Serum chemistry will include creatinine, blood urea nitrogen, glucose, lactate dehydrogenase, uric acid, total cholesterol, total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase. Urinalysis will include specific gravity, pH, glucose, ketones, blood, protein, nitrite, leukocyte esterase, urobilinogen, and bilirubin. In case the urine dipstick test result is abnormal, a urine sample should be sent into the central laboratory for microscopic examination.

l Clinical laboratory testing at screening visit (Visit 1) will include hepatitis screen covering HBs Ag, HBs Ab, HBc Ab, HCV Ab, HIV screen (Anti-HIV-1 and HIV-2 antibodies). In case of results showing HBs Ag (negative) and HBc Ab (positive), an HBV DNA testing will be performed and should be confirmed negative prior to randomization. In case of results showing HCV Ab (positive), an HCV RNA testing will be performed and should be confirmed negative prior to randomization.

m Only for women of childbearing potential. Pregnancy will lead to definitive treatment discontinuation in all cases. Pregnancy testing should be done monthly, female participants will be supplied with dipsticks for months with no study center visits planned. In female participants who discontinue the study intervention, the pregnancy testing should continue for a minimum of 12 weeks after the last dose of study intervention. In between visit, urine pregnancy tests must be performed at home. For urine pregnancy tests performed at home, female participants will have to complete a pregnancy test diary.

n Serum dupilumab concentration and ADA samples will be collected and archived prior to administration of IMP. In the event of any SAE, any AE of severe injection site reaction lasting longer than 24 hours, or any AESI of anaphylactic reaction or systemic allergic reaction that is related to IMP and require treatment, PK and ADA samples will be collected at or near the onset of the event for any additional analysis if required or for archival purposes.

o For participants (with exception of adolescents) who decide to participate and provide a specific written informed consent for the optional basophil activation test at selected sites in US and Canada only.

p For participants (with exception of adolescents) who decide to participate and provide a specific written informed consent for the optional archive serum and plasma sample. Archive serum and plasma samples (optional) are collected for future analysis of potential biomarkers of drug response, disease activity, safety and the type 2 inflammation pathway.

q For participants (with exception of adolescents) who decide to participate and provide a specific written informed consent for the optional genomics sub-study (DNA sample collection). The DNA sample should be collected at the Day 1 visit but can be collected at any visit during the study.

r For participants (with exception of adolescents) who decide to participate and provide a specific written informed consent for the optional genomics sub-study (RNA sample collection). The RNA sample must be collected before the administration of the first dose of IMP and at Week 24 before the administration of the IMP.

s Positive provocation test defined as presence of at least a confluent hive/wheal at the entire skin site of exposure after ice cube provocation test.

t The Wheal intensity Likert scale for wheal intensity after provocation test will be completed by the Investigator after the provocation test and entered in the eCRF.

u Participants will complete the DLQI (≥16 years old) or CDLQI (≥12 to <16 years old).

v HCRU (missed school/workdays) baseline version to be administered at baseline; postbaseline version to be administered at the subsequent visits. It will be entered in the eCRF.

2 INTRODUCTION

Chronic urticaria comprises CSU and CIndU, and both are characterized by the appearance of itchy wheals (hives), angioedema, or both that reoccur for more than 6 weeks. The symptoms occur either without a specific trigger in the case of CSU, or are induced (provoked) by a specific and definite trigger in the case of CIndU (1, 2). There are 9 subtypes of CIndUs depending on the type of trigger that provokes urticaria signs and symptoms: symptomatic dermographism, ColdU, DPU, solar urticaria, heat urticaria, vibratory angioedema, CholU, contact urticaria, and aquagenic urticaria. Most CIndU subtypes are rare and the most common are symptomatic dermographism, ColdU (also called chronic inducible cold urticaria) and CholU (1).

Chronic inducible ColdU is the second most common form of physical urticaria (1, 14). Cold urticaria is a relatively rare disorder with a reported prevalence of 0.05% as per one study in Europe (4), with a higher prevalence in northern climates. It is also self-limited, lasting 4 to 5 years on average (5). Chronic inducible ColdU often develops in young adults and is diagnosed based on the patient history and the results of provocation testing. Systemic symptoms of mast cell activation may occur, and up to 35% to 70% of patients with chronic inducible ColdU have experienced systemic reactions including anaphylaxis in severe cases (4).

Therapy is focused on the avoidance of the trigger factor and symptomatic treatment. The consensus recommendations for CIndU management (EAACI/GA²LEN/EDF/UNEV) (1) are mainly based on treatments approved for CSU, and some clinical data available in patients suffering from various types of CIndUs (cholinergic, symptomatic dermographism, ColdU). The recommended therapies are, in general, not approved for CIndU by regulatory agencies, with only limited specific countries where antihistamines are approved under broader “urticarial” indications. All patients are advised to avoid prolonged skin contact with cold objects or exposure to cold air temperature for CIndU, a similar stepwise approach as in patients with CSU is recommended: second-generation H1-antihistamines are the first-line (standard doses) and second line (high doses) therapies, although there is a lack of good evidence in patients with CIndU for the latter recommendation. Approximately 50% of patients achieve symptomatic control with conventional H1-antihistamine therapy, defined as reduction of hives and itch (15). Step 3and 4 of treatment options include omalizumab and ciclosporin A, respectively. Omalizumab, a monoclonal anti- IgE antibody, is the most used off label treatment in antihistamine-resistant patients with CIndU including ColdU. However, approximately a third of the patients treated with omalizumab are not well-controlled (16).

Chronic inducible ColdU is debilitating and severely affects patients QoL. Avoidance of offending triggers poses massive changes to everyday life and therefore is typically not feasible. Thus, the need for treatment options is high, especially as no approved treatments are available.

The underlying pathologic mechanism, while not well understood, is thought to be driven by mast cell activation and degranulation. Activation of skin mast cells with the release of histamine and other pro-inflammatory mediators leads to the signs and symptoms of CIndUs. Increased numbers of mast cells are found in both lesional and non-lesional skin in CSU and inducible urticaria. Interleukin-4 and IL-13, causative cytokines of type 2 inflammation, are secreted by mast cells in

addition to T helper 2 (Th2) lymphocytes. Mast cells express the IL-4 receptor, IL-4Rα, which is also stimulated by IL-13. Stimulation of mast cell IL-4Rα has been shown to also promote degranulation, adhesion, and chemotaxis, and to enhance FcεRI expression (4, 17).

Dupilumab is a human mAb directed against the IL-4Rα, which is a component of IL-4 receptors Type I and Type II, the latter being also a receptor for IL-13. The binding of dupilumab to IL-4Rα results in blockade of both IL-4 and IL-13 signaling. As a targeted immunomodulatory agent, dupilumab selectively inhibits the type 2 immune response, including Th2 cells, which can potentially achieve the desired therapeutic effect without the side effects typically associated with the use of broad immunosuppressants. The type 2/Th2 pathway is responsible for several pathophysiological mechanisms including mast cell and basophil degranulation. Dupilumab has shown efficacy in multiple diseases with underlying type 2 inflammation such as AD, asthma, CRSwNP, and EoE. In these clinical studies, treatment with dupilumab resulted in continuous decreases in blood total IgE. Moreover, in CRSwNP studies, a decrease in urinary LTE4 and PGDM was reported, suggesting that dupilumab has impact on mast cell functions.

Based on the above described dupilumab mechanism of action as well as available data with dupilumab, this study will evaluate dupilumab efficacy in patients with primary acquired chronic inducible ColdU.

2.1 STUDY RATIONALE

Primary acquired chronic inducible ColdU patients with and without angioedema experience hives and pruritus secondary to mast cell dysregulation. Degranulation of mast cells in CIndu is held to be mediated by FcεRI activation, through cell surface-bound IgE cross-linked by as of yet unidentified autoallergens. The subsequent release of histamine and other pro-inflammatory mediators leads to local tissue edema and pruritus. While antihistamines are the mainstay of therapy, not all patients are controlled with antihistamines alone, and not all antihistamine-refractory patients are adequately responsive to omalizumab (anti-IgE antibody) therapy. Therefore, there remains an unmet need. One possible way to meet this need is through novel therapies that target signaling pathways important for mast cell and basophil survival and function. Interleukin-4/IL-13 signaling is required for antibody isotype switching to IgE production in B cells and contributes to mast cell survival and function (4, 7). Therefore, blockade of IL-4/IL-13 by dupilumab represents a novel therapeutic approach for chronic urticaria patients. In a small case series of patients who had concurrent AD and CSU and were resistant to omalizumab, treatment with dupilumab improved their urticaria (12). The same has been observed in 1 patient with chronic inducible ColdU (13). These data further support the rationale to target IL-4/IL-13 signaling with dupilumab in patients with chronic urticaria. As this is a novel therapy that acts further upstream than IgE -targeted therapies, the clinical study proposed here will test the efficacy of dupilumab in patients who have failed antihistamines alone.

Based on the known pharmacokinetics (PK), safety and efficacy of dupilumab, the selected dosing regimen is dupilumab 300 mg q2w with a loading dose of 600 mg for adults; and 300 mg q2w with a loading dose of 600 mg for adolescents >60 kg at baseline OR 200 mg q2w with a loading dose of 400 mg for adolescents ≥30 kg and <60 kg at baseline. To achieve effective drug concentrations rapidly and thereby allowing a rapid clinical and pharmacodynamics (PD)

response, a loading dose is selected for this study as done in the dupilumab AD program. These are the approved dose regimens for AD, another skin disease and they are expected to achieve concentrations in serum that saturate the IL-4/IL-13 receptor in most patients, and hence they are expected to provide the maximum benefit and therefore to achieve the optimal benefit/risk ratio in this patient population. The same dosing regimens are currently under investigation in a dupilumab Phase 3 study in patients with CSU who remain symptomatic despite the use of H1-antihistamine treatment.

The study is designed to test the hypothesis that dupilumab is effective in inhibiting hives/wheals after provocation test (ice cube provocation test), in patients suffering from primary acquired chronic inducible ColdU who remain symptomatic despite the use of H1-antihistamine treatment.

2.2 BACKGROUND

Chronic inducible ColdU is a debilitating condition that severely affects QoL. It is normally not feasible to avoid the offending trigger without significant changes to everyday life. The majority of patients with chronic inducible ColdU may experience systemic reactions, including anaphylaxis in severe cases. There is no approved treatment available to date for chronic inducible ColdU, and EAACI/GA²LEN/EDF/WAO guidelines treatment recommendations (2) are mainly based on the approved treatments for CSU. Many patients however are refractory to these treatments; therefore, a high unmet medical need exist.

In the EFC16720 study the target population consists of patients with primary acquired chronic inducible ColdU who remain symptomatic despite treatment with H1-antihistamine as these patients have a significant unmet medical need. The updated international guideline on the definition, classification, diagnosis, and management of urticaria (1, 2) provides recommendations and a treatment algorithm. Steps 1 and 2 of this algorithm is the use of non-sedating H1-antihistamines at approved, or increased doses (up to 4-fold), respectively. Step 3 and 4 of treatment options include omalizumab and ciclosporin A, respectively. This protocol allows the use of H1-antihistamine at up to 4-fold the approved doses as background medication at stable doses.

2.3 BENEFIT/RISK ASSESSMENT

The Sponsor recognizes that the “Coronavirus Disease 2019” (COVID-19) pandemic may have an impact on the conduct of clinical trials. The Sponsor will monitor the situation closely and ensure the integrity of the trial conduct and data (see Appendix 9 [Section 10.9]).

More detailed information about the known and expected benefits and risks and reasonably expected AEs of dupilumab are available in the Investigator’s brochure (IB).

2.3.1 Benefit assessment

Dupixent (dupilumab) is authorized for marketing in over 50 countries worldwide including the United States (US), European Union (EU) (Centralized Procedure), Japan, China, Canada, and

Australia for adult AD indication. Dupilumab is also authorized in the US, EU, and other jurisdictions for the adolescent AD indication, and in the US, EU, Japan and other jurisdictions for the adult and adolescent asthma indication. Dupilumab also has approval for its CRSwNP indication in the US, EU, and Japan.

The target population of EFC16720 are patients with chronic inducible ColdU who remain symptomatic despite the use of H1-antihistamine treatment. These patients have failed antihistamine therapy and have active disease as indicated in Section 5. There are currently no therapies that are approved specifically for the treatment of cold-induced urticaria. Therefore, these patients have a high unmet medical need for novel effective treatment. Participation in EFC16720 will provide an opportunity for these patients to be treated with dupilumab that has proven efficacy in disease states (eg, AD, asthma, CRSwNP) where type 2 inflammation is the underlying driver of the disease process, and which targets signaling pathways important for mast cell survival and function that may provide a new treatment option for chronic inducible ColdU.

Interleukin-4 is essential for the function/survival of several cell types important in the pathogenesis of urticaria, including B cells, Th2 cells, mast cells, and basophils (12, 18, 19, 20, 21, 22). It is hypothesized that dupilumab will be effective in reducing itch and hives and improve angioedema urticaria control as well as QoL, in adults and adolescents with CSU and chronic inducible ColdU. Supporting the mechanistic rationale for dupilumab's potential effectiveness in CSU, dupilumab improved the hives and itch severity/frequency in a case series of 6 patients with CSU (12). Ferrucci et al reported (13) that a patient with chronic inducible ColdU who failed to respond to omalizumab (anti- IgE antibody) and oral cyclosporine, healed shortly after starting dupilumab. Itch (Numerical Rate Scale) and QoL (Dermatology Life Quality Index [DLQI]) significantly improved in this patient after only 1 month of therapy with dupilumab and the ice cube provocation test was negative. The patient underwent cold-water exposure by rafting in a mountain river (water temperature 3°C), without showing any relapse of urticaria.

The participants who will participate in this study may have the potential benefit of receiving a novel treatment for the underlying disease process. Based on the dupilumab mechanism of action in reducing IgE production and effects on mast cells mediators, it is anticipated that use of dupilumab will lead to reduced signs and symptoms associated with primary acquired chronic inducible ColdU and improved function and QoL for these participants.

Treatments approved in CSU are antihistamines or omalizumab. In general, treatments for chronic inducible ColdU including omalizumab are given off label. Thirty-five percent to 70% of patients with chronic inducible ColdU have experienced systemic reactions including anaphylaxis in severe cases. Thus, the need for approved treatment options for chronic inducible ColdU is high (4).

One possible way to meet this need is through novel therapies that target signaling pathways important for mast cell and basophil survival and function. Interleukin-4/IL-13 signaling is required for antibody isotype switching to IgE production in B cells and contribute to mast cell and basophil survival and function. Therefore, blockade of IL-4/IL-13 by dupilumab represents a novel therapeutic approach for chronic inducible ColdU patients.

This 24-week study allows for assessment of the effect of dupilumab on urticaria symptoms after the cold provocation test (hives/wheals, itch, pain, and burning sensation), and on participant's HRQoL, and health status.

2.3.2 Risk assessment

No tissue targets or specific hazards to humans were identified in nonclinical general and reproductive toxicology studies.

Dupilumab has an extensive safety database. As of 28 March 2020 (Data Lock Point), 10 191 subjects were enrolled into the development program for dupilumab and are included in the safety population: 382 as healthy volunteers, 4405 from AD studies, 3614 from asthma studies, 782 from CRSwNP studies, 232 from EoE studies, 248 from the grass allergy and peanut allergy studies, 511 from the chronic obstructive pulmonary disease (COPD) studies, 5 from prurigo nodularis (PN) studies, and 12 from the CSU studies. The number of subjects exposed to dupilumab in clinical studies was 8720 (356 in healthy volunteer studies, 4052 in AD studies, 3263 in asthma studies, 470 in CRSwNP studies, 166 in EoE studies, 148 in the grass allergy and peanut allergy studies, 256 from the COPD studies, 3 from PN studies, and 6 from the CSU studies).

Based on clinical studies in AD, the safety profile in adolescent patients (ie, 12–17 years of age) appears similar to that of adults with AD. As of 28 September 2019, 336 adolescents had been exposed to dupilumab in AD clinical studies, with a total of 457.7 person-years of exposure.

Based on the sales figures and using the World Health Organization's defined daily dose for dupilumab of 21.4 mg/day, the cumulative post-marketing exposure to dupilumab is estimated to be 161 582 patient-years (01 January 2017 to 31 March 2020).

Dupilumab has been generally well-tolerated in all populations tested in clinical development programs consistent with a positive benefit/risk profile. The adverse drug reactions (ADRs) identified to date for dupilumab include injection site reactions, conjunctivitis (including allergic and bacterial), oral herpes, herpes simplex, blepharitis, keratitis, dry eye, eye pruritus, eosinophilia, serum sickness, anaphylactic reaction, angioedema, and arthralgia. These ADRs were generally mild or moderate, transient, and manageable. These ADRs were not consistently observed in all indications (see IB for greater details). More significant serious allergic reactions were very rare. The ADRs reported in the post-marketing setting include events of anaphylactic reaction, angioedema, arthralgia, keratitis, and ulcerative keratitis. Importantly, no increased overall infection risk was observed in patients treated with dupilumab.

Systemic hypersensitivity has been established as an important identified risk with dupilumab. As protein therapeutics, all mAbs are potentially immunogenic. Rare serious and systemic hypersensitivity reactions have been observed in the dupilumab program including serum sickness/serum sickness-like reaction in the adult AD program and anaphylaxis related to dupilumab in the adult asthma clinical studies.

The important potential risk for dupilumab is "eosinophilia associated with clinical symptoms in asthma patients." The observed increase in eosinophil count is transient, which is consistent with

the current understanding of the mechanism of action of dupilumab. In dupilumab asthma studies, a small number of patients with asthma experienced serious systemic eosinophilia presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis, conditions which are often treated with systemic corticosteroids (SCS) therapy. These events have been seen in other drug development programs for severe asthma and usually, but not always, have been associated with the reduction of oral corticosteroid therapy suggesting possible unmasking of these conditions with tapering of corticosteroids during dupilumab therapy. The association of dupilumab treatment and these events has not been established. Health care providers should be alert to eosinophilia associated with vasculitis rash, worsening of pulmonary symptoms, pulmonary infiltrate, cardiac complications, and/or neuropathy presenting in their patients, especially upon reduction of SCS.

Patients with known helminth infections were excluded from participation in clinical studies, therefore it is not known if dupilumab will influence the immune response against helminth infections. Consequently, patients with pre-existing helminth infections should be treated for their helminth infection before initiating therapy with dupilumab.

The common ADR across all indications is injection site reaction. Other potential risks based on the safety profile in particular indications are discussed in the IB.

To date, the safety profile has been similar among adult and adolescent patients in asthma and AD populations and adult patients with CRSwNP. While long-term data are still accumulating, data from randomized, placebo-controlled trials and open-label extension studies to date, have not identified any new safety concern in these populations. It is anticipated that dupilumab in patients with primary acquired chronic inducible ColdU will have a favorable safety profile as observed across other type 2-driven immunological disorders.

2.3.3 COVID-19 Benefit-risk assessment

Dupilumab has shown clinical benefit in several type-2 driven immunological disorders, such as AD, asthma, and CRSwNP. In asthma and AD, clinical benefit has also been established in certain pediatric patients (asthma in adolescents and AD in 6 to18 years old) and a similar benefit-risk profile to adults has been observed.

To date, more than 8000 patients have been treated with dupilumab during the clinical development program in several indications, of which AD, asthma, and CRSwNP are licensed in some countries.

Currently, as sufficient data in patients with COVID-19 who are being treated with dupilumab is not available. Thus, the safety and efficacy of dupilumab in COVID-19 patients are unknown. During the course of the clinical trial program, respiratory infections including viral infections were monitored and these events are not listed as ADRs with dupilumab.

The target population of EFC16720 are participants with primary acquired chronic inducible ColdU have uncontrolled disease and in general, treatments for chronic inducible ColdU including omalizumab are given off label. Therefore, these patients have a high unmet medical need for novel effective treatment. Participation in EFC16720 will provide an opportunity for these

patients to be treated with a novel therapy that has proven efficacy in certain other disease states (ie, AD, asthma, CRSwNP), where type 2 inflammation is the underlying driver of the disease process.

Based on the aforementioned potential benefits to patients participating in EFC16720, the Sponsor's assessment is that the benefit-risk remains favorable for the participants to participate in this study.

2.3.4 Overall benefit: risk conclusion

Based on the evidence to support the potential therapeutic benefit in patients with primary acquired chronic inducible ColdU, a patient population with an unmet medical need, considering the favorable benefit/risk profile across multiple indications, and the extensive available safety database, the Sponsor is proposing to conduct a Phase 3 program with dupilumab for the treatment of patients with cold-induced urticaria.

3 OBJECTIVES AND ENDPOINTS

Table 2 - Objectives and endpoints

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
Tertiary/exploratory	
[redacted]	
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

3.1 APPROPRIATENESS OF MEASUREMENTS

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 (4). The assessments used in this study focus on evaluation of local symptoms that occur after skin contact to cold using ice cube provocation test. In addition, overall urticaria control, daily documentation of skin reactions to cold, participant's QoL, reduction in need of rescue therapy and health status are evaluated.

The proposed primary endpoint is proportion of participants with negative ice cube provocation test (absence of a confluent hive/wheal at the entire skin site of exposure) at Week 24. Cold provocation tests are standard in diagnosis of cold urticaria (4). In addition, they are used for assessment of efficacy in clinical trials (23, 24) in patients with ColdU. Cold urticaria symptoms appear only after skin contact with a cold trigger (cold air, liquids, or solid objects), usually within minutes, and persist for up to a few hours. The use of cold provocation tests allows for the standardization of the cold trigger and for performing assessment in predefined time points. The ice cube provocation test will be standardized for the purpose of this study and an operational manual with instructions for ice cube preparation and cold provocation test administration will be provided to the study centers along with the study protocol. This will ensure that all study centers will apply the ice cube provocation tests consistently across this international, multi-center clinical study.

Presence of a confluent hive/wheal as well as wheal intensity will be assessed by the clinicians 10 minutes after removal of the ice cube, as recommended in the CIndU (EAACI/GA²LEN/EDF/UNEV) guidelines (1). Assessment will be performed at each provocation test, ie, at Week 0, Week 12, and Week 24. In addition, symptoms of itch severity, skin burning sensation, and skin pain will be assessed by the participant 10 minutes after the cold provocation test.

The clinical picture of a participant at the time of study visits may not be totally representative of the actual current disease status due to symptom fluctuation that is dependent upon the contact with the triggering temperature. Therefore, the participants will rate the disease activity using the ColdUAS questionnaire in an e-diary. On a daily basis, participants will report their skin reactions (wheals and swelling), skin sensations (itching, burning, pain or feeling hot), avoidance behavior and trigger exposure, and overall symptoms severity. Cold Urticaria Activity Score will provide important supportive information on clinical improvement of the participants on a daily basis. Since skin reactions, skin sensations and behavioral avoidance to trigger vary from one day to another, ColdUAS will be assessed on a daily basis.

Participants with primary inducible ColdU are at risk of developing systemic hypersensitivity reactions including anaphylaxis after exposure to cold triggers. Such systemic reactions are mainly described as provoked by aquatic activities (eg, swimming in cold water) when the whole body, or a large proportion of it, was in contact with cold. Systemic hypersensitivity events will be documented via adverse event of special interest (AESI)/serious adverse event (SAE) reporting, and information about corrective treatment will be collected.

To get a complete picture of the disease, it is important to assess disease control over the course of treatment in addition to urticaria symptom assessment. Patients are best positioned to accurately assess this control, as they experience and feel it. They will self-assess their ColdU control using the urticaria control test (UCT), a well-developed and validated instrument in chronic urticaria patients (25).

Lastly, patients with primary acquired chronic inducible ColdU experience substantial HRQoL impairment. Therefore, the DLQI, a dermatology-specific instrument designed to assess HRQoL in adults ≥16 years old (26) with dermatologic conditions, and the corresponding Children's Dermatology Life Quality Index (CDLQI) for adolescents aged ≥12 years to <16 years old will be used, in addition to the newly developed disease-specific Cold Urticaria Quality of Life (ColdU-QoL) questionnaire..

The proposed primary and secondary endpoints will answer important clinical questions about the efficacy of dupilumab on disease symptoms, disease control and HRQoL in patients with primary acquired chronic inducible ColdU.

4 STUDY DESIGN

4.1 OVERALL DESIGN

The EFC16720 study is a 24-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center study to evaluate the use of dupilumab in adults and adolescents (≥12 to <18 years old) with primary acquired chronic inducible ColdU who remain symptomatic despite the use of H1-antihistamine. Participants using H1-antihistamine regularly/daily or as needed are eligible since both treatment regimens are common in patients with ColdU (5). The study is designed to test the hypothesis that dupilumab will increase the 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 hive/wheal at the entire skin site of exposure after an ice cube provocation test.

The study consists of 3 periods:

- Screening period (2 to 4 weeks).
- Randomized IMP treatment period (24 weeks).
- Post IMP treatment period (12 weeks).

Chronic inducible ColdU signs and symptoms will be evaluated after an ice cube provocation test, by the Investigator (hives/wheals intensity) and participant (itch severity, skin pain, skin sensation). In addition, chronic inducible ColdU disease activity will be assessed daily by the participant using ColdUAS questionnaire in an e-diary where the participant will report his/her skin reactions (wheals and swelling), skin sensations (itching, burning, pain or feeling hot), if they have been in contact with cold temperatures that usually cause skin reactions, if they have avoided trigger exposure, and overall symptoms severity. The study will also assess the effect of dupilumab on urticaria control, participants´ HRQoL and overall health status, proportion of patients with cold urticaria requiring emergency medical care visit or treatment with epinephrine and on reduction of rescue therapy.

The total anticipated number of participants randomized in the study is 78. This corresponds to approximately 39 participants who will be randomly assigned to each intervention arm:

- Dupilumab: 300 mg every q2w for adults; 200 mg q2w for adolescents ≥30 kg and <60 kg at baseline or 300 mg q2w for adolescents ≥60 kg at baseline.
- Matched placebo.

At least 4 participants randomized in the study will be adolescents (≥12 to <18 years old) who will be recruited in a few selected sites in selected countries. Randomization will be stratified by age (adolescent versus adult) and within adult group by country and background H1-antihistamine regular/daily use (Yes/No) (see Section 6.1.2 for additional background therapy details).

Number of participants using H1-antihistamine as needed prior to study entry should be at least [redacted].

During the study, participants should continue their established standard of care background therapy with a long-acting non-sedating H1-antihistamine, at up to 4-fold the approved dose for CSU.

- Participants who used H1-antihistamine regularly/daily prior to study entry should continue to take it daily. Note: regular/daily use of H1-antihistamine prior to study entry is defined as H1-antihistamine intake for at least 4 days per week for at least 1 month prior to screening visit (Visit 1)
- Participants who took H1-antihistamine as needed prior to study entry should limit the use to short-term.

The H1-antihistamine dose used during the study should be the same dose the participants took to prevent ColdU symptoms prior to study entry ("prescreening dose"). However, if participants experience a flare rescue therapy may be initiated. Please refer to Section 6.5.1 for rescue therapy.

If participants are on a dose higher than 4-fold the approved CSU dose at the screening visit (Visit 1), the Investigator can adjust the participant's dose within the stipulated range at the screening visit (Visit 1).

All participants will be allowed to take study-defined H1-antihistamine as rescue therapy as long as they do not exceed 4-fold the approved CSU dose during screening, treatment, and follow-up periods. If symptoms are still uncontrolled after increase of H1-antihistamine to the maximum allowed dose, or if the participant is already on the 4-fold approved dose of H1-antihistamine, participants can switch to another antihistamine up to 4-fold (2-fold in Japan) the approved dose for CSU or a short course of oral corticosteroids (OCS) is allowed during the treatment and follow-up periods. For rescue therapy in participants in Japan, please see Appendix 8 (Section 10.8). However, for the purpose of the primary analysis, data collected after OCS use will be set to missing and the worst postbaseline value before OCS will be used.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

In the EFC16720 study the target population consists of patients with primary acquired chronic inducible ColdU who remain symptomatic despite treatment with H1-antihistamine alone as these patients have a significant unmet medical need. Therapy for the patients is focused on the avoidance of the trigger factor and symptomatic treatment. The updated international guideline on the definition, classification, diagnosis and management of urticaria (1, 2) provides recommendations and a treatment algorithm. The consensus recommendations for CIndU management are mainly based on treatments approved for CSU, and some clinical data available in patients suffering from various types of CIndUs (cholinergic, symptomatic dermographism, ColdU). The recommended therapies are, in general, not approved for CIndU by regulatory agencies, with only limited specific countries where antihistamines are approved under broader "urticaria" indications. A similar stepwise approach as in patients with CSU is recommended for CIndU, including ColdU. Steps 1 and 2 of this algorithm is the use of non-sedating H1-antihistamines at approved, or increased doses (up to 4-fold), respectively. Step 3and 4 of treatment options include omalizumab and ciclosporin A, respectively. More than 50% of acquired primary chronic inducible cold urticaria patients do not respond to H1-antihistamine

treatment (8). Omalizumab, a monoclonal anti- IgE antibody, is the most used off label treatment in antihistamine-resistant patients with CIndU including ColdU. However, approximately a third of the patients treated with omalizumab are not well-controlled (12).

Study EFC16720 targets patients not adequately controlled with H1-antihistamine treatment and allows the use of H1-antihistamine at up to 4-fold the approved doses as background medication at stable doses.

As mentioned in Section 2.1 dupilumab at SC doses of 300 mg and 200 mg have been observed to suppress both total and antigen specific IgE levels across the indications studied: AD, asthma, and CRSwNP. In addition, dupilumab offers a new mechanism of action by inhibiting IL-4 signaling via the Type I receptor and both IL-4 and IL-13 signaling through the Type II receptor. Blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13, key cytokines that drive optimal mast cell degranulation and IgE production and other type 2 inflammatory responses, including the release of pro-inflammatory cytokines, chemokines, nitric oxide, and IgE (21).

There are a limited number of studies conducted in patients with cold urticaria. As mentioned above, the guideline recommendations for CSU are adopted for patients with CIndU; however, there are several differences between CSU and CIndU. In CIndU, the symptoms only occur after skin exposure to physical or chemical triggers. The duration of individual wheals is often relatively brief for CIndU, lasting minutes to hours. This is the reason why different assessment tools and endpoints are used in CIndU clinical studies compared with CSU. Cold provocation tests are used in clinical studies in patients with chronic urticaria to evaluate efficacy of treatments, mainly antihistamine treatments, but also doxepin, cyproheptadine (4), either by evaluating proportion of patients who after treatment did not develop signs/symptoms with the cold provocation test or evaluating the response to an experimental cold-simulation time test (CSTT) ie, minimum time threshold of cold stimulation required to induce a coalescent wheal and other cold urticaria signs and symptoms. This study will assess efficacy using the primary endpoint of the proportion of participants with negative ice cube provocation test at Week 24. The patients/Investigators will also score local signs and symptoms before and after provocation test assessing effect of the IMP on hives, itch, burning sensation, and pain. Ice cube provocation test is a traditional test used in common practice. For the study, the method will be standardized and compliant with according to the International EAACI/GA^{2}LEN/EDF/UNEV guidelines (1). In addition to provocation test, cold urticaria signs and symptoms will be evaluated using ColdUAS. It is scored by patients daily to assess overall disease activity.

A large portion of patients with ColdU (35% to 70%) have experienced systemic reactions including anaphylaxis, after extensive cold exposure and exercise, respectively (4). Avoidance of offending triggers poses massive changes to everyday life and therefore is typically not feasible. This has significant impact on patients´ QoL. The study will assess the proportion of patients with cold exposure triggered urticaria requiring emergency medical care visit or treatment with epinephrine urticaria.

A double-blind, randomized, placebo-controlled design is chosen to minimize bias in data collection and interpretation. The presence of a placebo arm is appropriate for the objectives of this study since it will provide the most robust assessment of the efficacy and safety of dupilumab. Rescue medication including epinephrine ensure that the safety or health of participants is not compromised. In addition to common safety measures implemented in the currently planned study

(per protocol Section 1.3 and Section 8.2), the Investigators will oversee efficacy via monitoring of ColdU symptoms collected daily in an e-diary and can continuously assess benefit and risk for each individual participant and decide about the need to administer rescue therapy (Section 6.5.1) or to discontinue the IMP. The study participants may withdraw from treatment if he or she decides to do so, at any time and irrespective of the reason.

The 24-week treatment duration should be sufficient for efficacy evaluation of dupilumab. Dupilumab treatment has shown clinical efficacy prior to Week 24 in all Phase 3 clinical studies examined across all indications. In addition, biomarkers of disease response, including total serum IgE levels plateau after Week 16 but before Week 24 in prior AD clinical studies, including the 52-week AD study (R668-AD-1224; CHRONOS). Given that the clinical efficacy and biomarker changes occur prior to Week 24 in prior studies in multiple indications, the Sponsor considers that a 24-week study is an appropriate duration to observe dupilumab's effect in ColdU. The duration of the 12-week follow-up period is based on the time expected for drug levels to reach zero (below the lower limit of quantification) in most participants after the last dose of dupilumab.

In addition to adults, the study will evaluate efficacy and safety in adolescents. It is reported that cold urticaria often develops in young adults (1) and therefore, it is considered important to make dupilumab available to adolescent without delay. It is planned to enroll at least 4 adolescent participants (9). Inclusion of both populations in one study is supported by the fact that ColdU is similar in adult and adolescent patients in terms of pathophysiology, clinical presentation and diagnostic procedures, and treatment guidelines (EAACI/GA^{2}LEN/EDF/WAO) are similar for both adult and adolescent population.

Assessment of dupilumab will provide efficacy data that can be used for positioning of dupilumab in current treatment algorithm of ColdU recommended in International Guideline (2).

4.3 JUSTIFICATION FOR DOSE

Based on the known PK, safety and efficacy of dupilumab, the selected dosing regimen is dupilumab 300 mg q2w with a loading dose of 600 mg for adults; and 300 mg q2w with a loading dose of 600 mg for adolescents ≥60 kg OR 200 mg q2w with a loading dose of 400 mg for adolescents ≥30 kg and <60 kg. These are the approved dose regimens for AD, another skin disease and they are expected to achieve concentrations in serum that saturate the IL-4/IL-13 receptor in most patients and hence they are expected to provide the maximum benefit and therefore to achieve the optimal benefit/risk ratio in this patient population. Organ perfusion is anticipated to be similar between AD and primary acquired chronic inducible cold urticaria and lower than the rate of lung perfusion.

Furthermore, for AD a loading dose was administered to more rapidly achieve effective drug concentrations, thereby allowing a rapid PD response as demonstrated by improvement in pruritus, a hallmark of AD. Similarly, as pruritus is a core symptom of primary acquired chronic inducible cold urticaria, and to achieve effective drug concentrations more rapidly, a loading dose is selected for this study.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all phases of the study including the last EOS Visit. If a participant discontinues the treatment period prematurely but completes follow-up to the planned EOS visit, he/she is considered a completer.

The overall EOS is defined as the date of the last visit of the last participant in the study.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

I 01. Participant must be ≥12 years to 80 years (or the minimum legal age for adolescents in the country of the investigational site) of age inclusive at the time of signing the informed consent. For those countries where local regulations do not permit enrollment of adolescents (≥12 years to <18 years of age), the recruitment will be restricted to those who are ≥18 years of age.

Type of participant and disease characteristics

I 02. Participants who have 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 screening visit (Visit 1).

I 03. Participants with positive ice cube provocation test, ie, presenting at least a confluent hive/wheal on the exposed skin area, at the screening visit (Visit 1) and randomization visit (Visit 2).

I 04. Participants meeting at least 1 of the following criteria despite regular/daily or as needed use of H1-antihistamine:

- Urticaria Control Test (UCT) (4-item) <12 at the screening visit (Visit 1) and randomization visit (Visit 2)
- Within 6 months prior to the screening visit, documented medical history of cold exposure triggered anaphylaxis or oropharyngeal edema
- Within 6 months prior to the screening visit, documented medical history of cold exposure triggered urticaria requiring emergency medical care visit or treatment with epinephrine.

I 05. Participants who are using a study-defined H1-antihistamine regularly/daily or as needed for primary acquired chronic inducible ColdU (see Section 6.1.2 for the list of antihistamines allowed for the study). Regular/daily use is defined as H1-antihistamine intake for at least 4 days per week for at least 1 month prior to screening visit (Visit 1).

Note: The participants who take H1-antihistamine regularly/daily should have the dose stable for at least 5 consecutive days prior to screening visit (Visit 1). The participants who

take H1-antihistamine as needed should not take H1-antihitamine for at least 5 consecutive days prior to screening visit (Visit 1).

Weight

I 06. Body weight ≥30 kg.

Sex

I 07. Male or Female

Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a) Female participants

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:
  - Is not a woman of childbearing potential (WOCBP).

  OR

  - Is a WOCBP and agrees to use a contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix 4 (Section 10.4) of the protocol during the study (at a minimum until 12 weeks after the last dose of study intervention).
  - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) on Day 1 before the first dose of study intervention.
  - If a urine test on Day 1 cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional details can be found in Appendix 4 (Section 10.4) of the protocol.
- The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

I 08. Capable of giving signed informed consent as described in Appendix 1 of the protocol which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. In countries where the legal age of majority is above 18 years old, a specific ICF must also be signed by the participant's legally authorized representative. For adolescents, both the adolescent and the parent/legally authorized representative must sign the specific ICF (Section 10.1.3 of the protocol).

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

E 01. Clearly defined underlying etiology for urticaria other than primary acquired chronic inducible ColdU. This includes but is not limited to the following urticarias:

- Acute urticaria
- Chronic spontaneous urticaria
- Inducible urticaria: all other forms of ColdU (acquired secondary ColdU, atypical acquired ColdU, hereditary ColdU syndromes), solar, cholinergic, heat, aquagenic, vibratory angioedema, symptomatic dermographism, delayed pressure, or contact.
- Diseases with possible symptoms of urticaria or angioedema: systemic lupus erythematosus, urticarial vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, hereditary or acquired angioedema, lymphoma, leukemia, or generalized cancer.

E 02. Systemic hypersensitivity reaction including anaphylaxis related or suspected to be related to ice cube provocation test at the screening visit (Visit 1) and randomization visit (Visit 2).

E 03. Presence of skin morbidities or associated with itch other than primary acquired chronic inducible ColdU that may interfere with the assessment of the study outcomes.

E 04. Participants having active AD.

E 05. 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.

E 06. History of human immunodeficiency virus (HIV) infection or positive HIV 1/2 serology at the screening visit (Visit 1).

E 07. Severe concomitant illness(es) that, in the Investigator's judgment, would adversely affect the participant's participation in the study. Examples include, but are not limited to participants with short life expectancy, participants with uncontrolled diabetes (hemoglobin A1c ≥9%), participants with cardiovascular conditions (eg, Class III or IV cardiac failure according to the New York Heart Association classification), severe renal conditions (eg, participants on dialysis), hepato-biliary conditions (eg, Child-Pugh class B or C), neurological conditions (eg, demyelinating diseases), active major autoimmune diseases (eg, lupus, inflammatory bowel disease, rheumatoid arthritis, etc), other severe endocrinological, gastrointestinal, metabolic, pulmonary, or lymphatic diseases. The specific justification for participants excluded under this criterion will be noted in study documents (chart notes, case report forms [CRFs], etc).

E 08. Known or suspected immunodeficiency, including history of invasive opportunistic infections (eg, tuberculosis [TB], histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, and aspergillosis) despite infection resolution, or otherwise recurrent infections of abnormal frequency or prolonged duration suggesting an immune-compromised status, as judged by the Investigator.

E 09. Participants with active TB or nontuberculous mycobacterial infection, or a history of incompletely treated TB will be excluded from the study unless it is well documented by a specialist that the participant has been adequately treated and can now start treatment with a biologic agent, in the medical judgment of the Investigator and/or infectious disease specialist. Tuberculosis testing will be performed on a country by country basis, according to local guidelines if required by regulatory authorities or ethics boards.

E 10. 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.

E 11. History of malignancy within 5 years before Visit 1, except completely treated in situ carcinoma of the cervix, completely treated and resolved nonmetastatic squamous or basal cell carcinoma of the skin.

E 12. Known or suspected alcohol and/or drug abuse.

E 13. History of systemic hypersensitivity or anaphylaxis to any other biologic therapy or any of its excipients.

E 14. Planned major surgical procedure during the participant's participation in this study.

E 15. Participant's with any other medical or psychological condition including relevant laboratory or ECG findings 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 study, may make participant's participation unreliable, or may interfere with study assessments. The specific justification for participants excluded under this criterion will be noted in study documents (chart notes, CRF, etc).

Prior/concomitant therapy

E 16. Participation in a prior dupilumab clinical study or have been treated with commercially available dupilumab.

E 17. Exposure to another systemic or topical investigative drug (mAbs as well as small molecules) within a certain time period prior to the screening visit (Visit 1), defined as follows: an interval of <6 months or <5 PK half-lives for investigative mAbs, whichever is longer, and an interval of <30 days or <5 PK half-lives, whichever is longer, for investigative small molecules.

E 18. Having used any of the following treatments within 4 weeks before the screening visit (Visit 1).

- Immunosuppressive/immunomodulating drugs (eg, systemic corticosteroids [oral or parenteral - intravenous, intramuscular, SC]), cyclosporine, mycophenolate-mofetil, interferon gamma, Janus kinase inhibitors, azathioprine, methotrexate, hydroxychloroquine, sulfasalazine, dapsone, colchicine, etc).
- Antifibrinolytic tranexamic acid and epsilon-aminocaproic acid.
- Leukotriene receptor antagonists (LTRAs) and H2 receptor antagonists. Note: patients taking stable LTRAs and/or H2 receptor antagonists for diseases other than CSU (eg, asthma or gastroesophageal reflux disease, respectively) will be permitted to continue their use.
- Phototherapy, including tanning beds.

E 19. Treatment with biologics as follows:

- Any cell-depleting agents including but not limited to rituximab: within 6 months before the screening visit (Visit 1).
- Anti-Ig E therapy (omalizumab) within 4 months before the screening visit (Visit 1).
- Other mAbs (which are biological response modifiers): within 5 half-lives (if known) or 16 weeks before the screening visit (Visit 1), whichever is longer.

E 20. Treatment with a live (attenuated) vaccine (Appendix 12 [Section 10.12] of the protocol) within 4 weeks before the screening visit (Visit 1).

NOTE: For participants who have vaccination with live, attenuated vaccines planned during the course of the study (based on national vaccination schedule/local guidelines), it will be determined, after consultation with a physician, whether the administration of vaccine can be postponed until after the EOS, or preponed to before the start of the study without compromising the health of the participant:

- Participants for whom administration of live (attenuated) vaccine can be safely postponed would be eligible to enroll into the study.
- Participants who have their vaccination preponed can enroll in the study only after a gap of 4 weeks following administration of the vaccine.

E 21. Routine (daily or every other day during 5 or more consecutive days) doses of doxepin within 14 days prior to the screening visit (Visit 1).

E 22. Planned or anticipated use of any prohibited medications (Section 6.5) and procedures during the screening and study treatment period.

E 23. Either intravenous immunoglobulin (IVIG) therapy and/or plasmapheresis within 30 days prior to the screening Visit (Visit 1).

Diagnostic assessments

E 24. Participants with any of the following result at the screening visit (Visit 1):

- Positive (or indeterminate) hepatitis B virus surface antigen (HBs Ag)HBs Ag or,
- Positive total hepatitis B core antibody (HBc Ab) confirmed by positive hepatitis B virus (HBV) Deoxyribonucleic acid (DNA) or,
- Positive hepatitis C antibody (HCV Ab) confirmed by positive hepatitis C virus (HCV) ribonucleic acid (RNA).

Noncompliance to completion of the e-diary

E 25. Participants are not complaint with completion of e-diary by completing entries on less than 4 days out of the 7 days immediately preceding the baseline visit (Visit 2).

Other exclusions

E 26. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 27. Any country-related specific regulation that would prevent the participant from entering the study.

E 28. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 29. Participants are employees of the clinical study center or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with Section 1.61 of the International Council of Harmonisation [ICH]-Good Clinical Practice [GCP] Ordinance E6).

E 30. Any specific situation during study implementation/course that may raise ethical concerns.

E 31. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

5.3 LIFESTYLE CONSIDERATIONS

Participants unwilling to attempt avoidance of known cold triggers.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants

to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants will be assigned a new participant number versus the 1 received for the initial screening visit (Visit 1).

5.5 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT/RANDOMIZATION/ADMINISTRATION OF STUDY INTERVENTION ADMINISTRATION

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures are proposed in Appendix 9 (Section 10.9) and should be considered for screening/enrollment/randomization/administration of study intervention.

6 STUDY INTERVENTION AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION ADMINISTERED

6.1.1 Investigational medicinal products

Table 3 - 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

ARM name	Dupilumab	Placebo
Packaging and labeling	Each dose of dupilumab will be supplied as 1 glass pre-filled syringe packed in a participant kit box. Both glass pre-filled syringe and box will be labeled as required per country requirement	Each dose of placebo will be supplied as 1 glass pre-filled syringe packed in a participant kit box. Both glass pre-filled syringe and box will be labeled as required per country requirement

Abbreviations: IMP = investigational medicinal product; NIMP = noninvestigational medicinal product.

The IMP is administered every 14 ±3 days (q2w) during the 24-week treatment period with the last IMP administration at Week 22.

The first IMP administration should be performed at the study center. Subsequent IMP administrations can be done at home by the participant (or parent/legally authorized representative, or caregiver). If the participant (or parent/legally authorized representative or caregiver) is unable or unwilling to prepare and inject IMP, injections can be performed at the study center by way of unscheduled visits; or arrangements can be made for qualified study center personnel and/or health care professionals (eg, visiting nurse service) to administer IMP at participant's home.

For doses not given at the study center, paper diaries will be provided to record information related to the injections. The paper diary will be kept as source data in the participants study file.

At Visit 2, the Investigator or delegate will prepare and inject the first dose of IMP in front of the participant (or parent/legally authorized representative, or caregiver). If home administration is planned, the participant (or parent/legally authorized representative or caregiver) will prepare and inject the second dose of IMP under the supervision of the Investigator or delegate. The training must be documented in the participant's study file. In case of emergency (eg, natural disaster, pandemic etc.) different training ways (eg, virtual training via video call etc.) can be performed (and will be documented in the participant's study file).

Subcutaneous injection sites should alternate between the upper thighs, 4 quadrants of the abdomen or the upper arms, so that the same site is not injected twice during consecutive administrations. Injection in the upper arms can only be done by a trained person (parent/legally authorized representative/caregiver trained by the Investigator or delegate) or health care professional but not the participants themselves.

Participants should be monitored for at least 30 minutes. The monitoring period may be extended as per country specific or local study center-specific requirements.

The participant/parent/legally authorized representative/caregiver should be trained by the study center staff to recognize potential signs and symptoms of hypersensitivity reaction in order to self-monitor/monitor at home for at least 30 minutes (or longer per country specific or local study center-specific requirements) following injection. In case of hypersensitivity symptom/s the participant should contact his/her healthcare provider/emergency contact.

The IMP may be supplied at the study center or from the Investigator/study center/Sponsor to the participant via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the participant.

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Appendix 9 (Section 10.9).

6.1.2 Noninvestigational medicinal product

During the study, participants should continue their established standard of care background therapy with a long-acting non-sedating H1-antihistamine, at up to 4-fold the approved dose for CSU.

- Participants who used H1-antihistamine regularly/daily prior to study entry should continue to take it daily. Note: regular/daily use of H1-antihistamine prior to study entry is defined as H1-antihistamine intake for at least 4 days per week for at least 1 month prior to screening visit (Visit 1)
- Participants who took H1-antihistamine as needed prior to study entry should limit the use to short-term.

The H1-antihistamine dose used during the study should be the same dose the participants took to prevent ColdU symptoms prior to study entry (“prescreening dose”). However, if participants experience a flare rescue therapy may be initiated. Please refer to Section 6.5.1 for rescue therapy.

If participants are on a dose higher than 4-fold the approved CSU dose at the screening visit (Visit 1), the Investigator can adjust the participant’s dose within the stipulated range at the screening visit (Visit 1).

The following list of H1-antihistamine is allowed as background and rescue therapy during the study (see Section 6.5.1) and noted with their recommended dose:

- Cetirizine 10 mg qd.
- Levocetirizine dihydrochloride 5 mg qd
- Ebastine 10 mg qd
- Fexofenadine 60 mg twice per day or 180 mg qd
- Loratadine 10 mg qd
- Desloratadine 5 mg qd
- Bilastine 20 mg qd
- Rupatadine 10 mg qd
- Other H1-antihistamine after discussion with the Sponsor.

For other information related to H1-antihistamine including safety precautions, please refer to the locally approved product labeling.

In each participant, all ice cube provocation tests from screening visit (Visit 1) to EOS (Visit 5) should be done under the same background therapy conditions. For at least 5 consecutive days prior to the test, participants should either be on stable H1-antihistamine prescreening dose (if they take H1-antihistamine regularly/daily) or be without H1-antihistamine intake (if they use antihistamine as needed). If needed the ice cube provocation test can be delayed in order to keep the conditions unchanged during the study.

Background therapy reimbursement will be provided when deemed necessary and as per country regulation.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Storage and Handling

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IMP received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants randomized in the study may receive IMP and only authorized study center staff may supply or administer IMP. At study center, all IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study center staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Responsibilities

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.8).

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party (except for direct-to-patient [DTP]shipment, for which a courier company has been approved by the Sponsor), allow the IMP to be used other than as directed by this clinical study protocol, or dispose of IMP in any other manner.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

All participants will be centrally assigned to randomized IMP using an interactive response technology (IRT). The Investigator will be questioned during the interactive voice response system (IVRS) phone call/interactive web response system (IWRS) web module if he/she wishes to enroll the participant in the study. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information and directions for the IWRS will be provided to each site.

At the screening visit (Visit 1), the Investigator or designee will contact the IRT system to receive the participant number. If a participant who had previously failed screening is approached for rescreening, a new ICF must be signed. In such case, a new participant number will be assigned by IRT.

Methods of assigning participants to treatment group

The randomized intervention kit number list is generated centrally by Sanofi and IMPs (dupilumab 300 mg, dupilumab 200 mg, or their matching placebo) are packaged in accordance with this list. The randomization and intervention allocation are performed centrally by an IRT. The IRT generates the participant randomization list and allocates the intervention number and the corresponding intervention kits to the participants according to it.

Participants will be randomized in a 1:1 ratio treatment arm as described in the Table 3.

Randomization will be stratified by age (adolescent versus adult) and within adult group by country and background H1-antihistamine regular/daily use (Yes/No) (see Section 6.1.2 for additional background therapy details).

Number of participants using H1-antihistamine as needed prior to study entry should be at least [redacted]. At screening (Visit 1), the Investigator or designee will contact the IRT system to receive the participant number. If a participant who had previously failed screening is approached for re-screening, a new ICF must be signed. In such case, a new participant number will be assigned by IRT.

A randomized participant is defined as a participant who has been allocated to a randomized intervention regardless of whether the treatment was administered or not (ie. participant registered by the IRT). A participant cannot be randomized more than once in the study.

Study intervention will be dispensed at the study visits summarized in schedule of activities (SoA) (Section 1.3). Returned study intervention should not be re-dispensed to the participants.

Methods of blinding

Dupilumab 300 mg/200 mg and placebo matching dupilumab 300 mg/200 mg will be provided in identically matched 2 mL/1.14 mL pre-filled syringes that are visually indistinguishable for each dose. Syringes and boxes will be labeled with a treatment kit number. Whilst this study is double-blinded in terms of treatment with either dupilumab or placebo, it is 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 will be used for the different weight categories for adolescents.

Code breaking

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted (eg, in case of available antidote). Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, he/she may, at his/her discretion, contact the Sponsor to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and the electronic case report form (eCRF), as applicable.

If the code is broken, the participant must withdraw from IMP administration.

6.4 STUDY INTERVENTION COMPLIANCE

- The Investigator or his/her delegate must ensure that IMP is administered to each participant according to the labeling instructions.
- Investigational medicinal product accountability:
  - Investigational medicinal product units are returned by the participant at each visit. In case of DTP process, the intervention units can be returned by the carrier (if defined in the contract).
  - The Investigator or his/her delegate counts the number of remaining kits/pre-filled syringes and fills in the Intervention Log Form.
  - The Investigator or his/her delegate records the dosing information on the appropriate pages of the eCRF.
  - The monitor in charge of the study then checks the eCRF data by comparing them with the IMP which he/she has retrieved and intervention log forms/source documents.
  - A paper diary will be dispensed to the participants for indicating IMP administration at home.

When participants are dosed at the study center, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study center staff other than the person administering the study intervention.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by checking diary and

used/unused kits/pre-filled syringes during the study center visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of kits/pre-filled syringes dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

6.5 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

Non-sedating H1-antihistamines, at up to 4-fold the approved dose for CSU, are allowed as background medication and on demand as recue medication. See Section 6.1.2 and Section 6.5.1 for details.

The concomitant use of the following therapies is prohibited during the entire study. Study treatment will need to be discontinued in participants receiving these treatments:

- 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.

  Note: a short course of OCS is allowed as rescue therapy (see Section 6.5.1)
- Any cell-depleting agents including but not limited to rituximab
- Monoclonal antibodies (which are biological response modifiers) including anti-IgE therapy (omalizumab)
- Treatment with a live (attenuated) vaccine
- IVIG
- Plasmapheresis
- Other investigational drugs.

The concomitant use of following therapies is prohibited during the entire study but study treatment will not need to be discontinued in participants receiving these treatments in violation of the protocol:

- Topical corticosteroids
- Topical calcineurin inhibitors
- Topical and oral antihistamines (other than those allowed as background or rescue therapy)
- Routine doses of doxepin (daily or every other day during 5 or more consecutive days)
- LTRAs and H2 receptor antagonists, unless stable and taken for diseases other than chronic inducible ColdU
- Antifibrinolytic tranexamic acid and epsilon-aminocaproic acid
- Phototherapy, including tanning beds.

6.5.1 Rescue medicine

All participants will be allowed to take study-defined H1-antihistamine (see Section 6.1.2) as rescue therapy as long as they do not exceed 4-fold the approved dose for CSU during the screening, treatment, and follow-up periods. If symptoms are still uncontrolled after increase of H1-antihistamine to the maximum allowed dose, or if the participant is already on the 4-fold approved H1-antihistamine, participants can switch to another antihistamine up to 4-fold the approved dose for CSU or a short course of OCS is allowed during the treatment and follow-up periods. In order to ensure consistency, when possible, it is recommended to use OCS for 5 to 7 days with a starting dose of oral prednisone 40 mg (or clinically comparable OCS) followed by taper per the Investigator's judgment.

Due to an episodic nature of ColdU, it is recommended to prescribe rescue therapy for a short period of time (not more than 7 days).

The ice cube provocation test should be delayed if rescue therapy (H1-antihistamine or OCS) is taken within 5 days prior to the test. The ice cube provocation test can be done when the participant is back to prescreening H1-antihistamine dose or is off H1-antihistamine (or OCS) intake for at least 5 consecutive days to allow to have ice cube provocation test performed under the same background condition for each participant from screening visit (Visit 1) to EOS (Visit 5).

In case of systemic hypersensitivity reactions due to cold, the participants may require epinephrine treatment. EpiPen (or a local equivalent) will be provided to the participants at the beginning of the study, and the participants should be appropriately trained how and when to use it. EpiPen use should be in accordance with the locally approved product labeling.

For rescue medication in participants in Japan, please see Appendix 8 (Section 10.8).

The initial background therapy should remain unchanged throughout the study. Participants should continue their prescreening dose of initial H1-antihistamine once rescue treatment is no longer required or stop H1-antihistamine intake. The use of permitted rescue medications should be delayed in all participants, if possible, for at least 8 weeks following the initiation of the investigational treatment. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

For other information including safety precautions related to H1-antihistamine, OCS, and EpiPen (or a local equivalent), please refer to the locally approved product labeling.

6.6 DOSE MODIFICATION

No change in IMP dose is allowed.

6.7 INTERVENTION AFTER THE END OF THE STUDY

The Sponsor will not be responsible for intervention after the EOS Visit. Intervention after the EOS Visit will be at the discretion of the Investigator or treating physician.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Definitive discontinuation

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant should complete the early treatment discontinuation visit with all assessments planned for the end of treatment (EOT) Visit. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention.

The participants may withdraw from treatment with the IMP if he or she decides to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reason(s) for treatment discontinuation, and this should be documented in the eCRF.

Participants must be permanently withdrawn from the study treatment for the following reasons:

- At their own request or at the request of their legally authorized representative (legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the patient's participation in the procedure(s) involved in the research).
- If, in the Investigator's opinion, continuation in the study would be detrimental to the participant's well-being.
- At the specific request of the Sponsor.
- In the event of a protocol deviation, at the discretion of the Investigator or the Sponsor.
- Any code broken requested by the Investigator will lead to permanent discontinuation of study intervention.
- Pregnancy.
- Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment (see Section 10.9).
- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin.
- Any opportunistic infection or other infections whose nature or course may suggest an immunocompromised status (see Section 10.11).
- Serum alanine aminotransferase (ALT) >3 × Upper Limit of Normal (ULN) and total bilirubin >2 × ULN (see Section 10.6).
- Serum ALT >5 × ULN if baseline ALT ≤2 × ULN or ALT >8 × ULN if baseline ALT >2 × ULN (see Section 10.6).

- If the participant develops a medical condition that requires use of prohibited medication (see Section 6.5).
- If the participant misses more than 2 consecutive doses of the IMP (see Section 7.1.2).
- Systemic hypersensitivity reaction including anaphylaxis related or suspected to be related to ice cube provocation test. In the participants who experienced such reaction no further ice cube provocation test should be done during the study.

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation within a reasonable timeframe as assessed by the Investigator before making a decision of definitive discontinuation of the IMP for the concerned participant.

If a clinically significant ECG finding is identified (including, but not limited to changes from baseline in QT interval corrected using [Bazett's formula {QTcB} or Fridericia's formula {QTcF}]) at screening, the Investigator or qualified designee will determine if the participant is eligible for the study. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

Handling of participants after definitive intervention discontinuation

Participants will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

Participants who discontinue the study intervention prematurely (prior to completing the 24-week treatment period) will perform, as soon as possible, the early treatment discontinuation Visit with all assessments normally planned for the EOT visit (Visit 4), to assure a complete clinical assessment in close temporal proximity to the premature termination of study treatment is available.

In addition, and to allow assessment of participant outcomes over the stipulated study period, participants will be asked and encouraged to complete all remaining study treatment visits and participate in safety follow-up according to the visit schedule with a ±3 day window. Under exceptional circumstances when a participant cannot come to the study center for a scheduled visit, a phone contact can be made. During the phone contact, at least information about AEs, concomitant medication and status of urticaria should be collected.

All cases of permanent intervention discontinuation must be recorded by the Investigator in the appropriate pages of eCRF when considered as confirmed.

7.1.2 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to regional or national emergency declared by

a governmental agency (Appendix 9 [Section 10.9]). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

In addition, if patients become infected while receiving treatment with dupilumab and do not respond to antihelminthic treatment, treatment with dupilumab should be temporarily discontinued until infection resolves.

If the participant misses more than 2 consecutive doses, the participant will be permanently discontinued from the study treatment.

For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

7.1.2.1 Rechallenge

Reinitiation of intervention with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned adverse event was unlikely and if the selection criteria for the study are still met (refer to Section 5.1 and Section 5.2).

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. Refer to SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study center records.

If participants no longer wish to take the IMP, they will be encouraged to remain in the study.

The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for Follow-up Visits and from withdrawal of consent for non-participant contact follow-up, (eg, medical record checks). The study center should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be re-randomized (treated) in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The study center must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).
- It is recommended that assessments/procedures at a study center visit are performed in the following order if applicable (see Section 1.3) and possible:
  - Patient-Reported Outcome questionnaires (ColdUAS [if not performed at home before the study visit], DLQI/CDLQI, UCT, ColdU-QoL, 5-level EuroQol 5-dimensional questionnaire [EQ-5D-5L]) should be completed by the participants before the consultation and/or clinical tests, in a quiet place. The questionnaires should be completed by the participants themselves, independently from their physician, the study nurse, or any other medical personnel and without any help from friends or relatives.
  - ECG (at screening), physical examination including vital signs, safety and laboratory assessment.
  - Ice cube provocation test.
  - Investigator/participant evaluation of urticaria symptoms at the provocation test site will be performed 10 minutes after ice cube removal. The Investigator will do his/her assessment first (the presence/absence of a confluent hive/wheal at the entire skin site of exposure [primary endpoint] and wheal intensity Likert scale). Then the participant will rate peak pruritus Numerical Rating Scale (NRS), peak burning sensation NRS, peak pain sensation NRS and will answer the Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC). It is important that the Investigator does not give any details of the evaluation to the participant, so his/her scoring and answers are not influenced by the Investigator's assessment.
- Adolescents complete the same PRO questionnaires as adults, except for the CDLQI (version adapted to adolescents). They may be helped by their parents/caregivers for the reading and the understanding of the instructions, a word or a question of the questionnaires if they encounter difficulties to answer. However, adolescents should answer the question themselves; parents/caregivers should not influence nor interpret their child's answer; parents/caregivers should not select any of the response choices on behalf of their child.

- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 160 mL. The maximum amount of blood collected from each adolescent over the duration of the study will not exceed 93 mL. The maximum amount of blood collected per each visit from each adolescent will not exceed 21 mL per visit. The maximum amount of blood collected from each adolescent per visit and within 4-week interval will be complaint with the European guideline (27). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

In light of the public health emergency related to COVID-19 (or in case of any other pandemic requiring public health emergency), the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms, eg, phone contact, virtual visits, online meetings, use of local clinic or laboratory locations, and home visits by skilled staff. Implementation of such mechanisms may differ country by country, depending on country regulations and local business continuity plans. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 (or any other pandemic) will be granted. All temporary mechanisms utilized, and deviations from planned study procedures are to be documented as being related to COVID-19 (or any other pandemic) and will remain in effect only for the duration of the public health emergency. For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

8.1 EFFICACY ASSESSMENTS

The e-diary is used for:

- Daily recording of the ColdUAS questionnaire
- Daily recording of H1-antihistamine medication use
- DLQI (≥16 years old)/CDLQI (≥12 to <16 years old), UCT, ColdU-QoL and EQ-5D-5L evaluation at the study center visit
- Assessment of peak pruritus NRS, peak burning sensation NRS, peak pain sensation NRS after provocation test.
- Assessment of PGIS and PGIC after participants have completed the NRS.

Timing of the assessment is specified in SoA (Section 1.3).

This device will be dispensed at the screening visit (Visit 1), including instructions for use and participants will be instructed on the use of the device.

Recorded information will be downloaded from this device daily. At the EOT visit, the e-diary will be downloaded and returned to the study center.

The study center staff regularly, and when alerts received, should check the status of the compliance to background therapy and overall e-diary compliance including ColdUAS. The study center should follow-up with the participant as appropriate.

Wheal intensity Likert scale and missed school/workday questionnaire will be filled in by the Investigator/study center staff in the eCRF.

8.1.1 Ice cube provocation test

Cold urticaria is defined by the appearance of its signs and symptoms (hives/wheals, itch, pain, and burning sensation) after contact cooling and rewarming of the skin. Chronic inducible urticarias, including primary acquired chronic inducible ColdU, are diagnosed based on the patient history and the results of provocation testing. Moreover, cold provocation tests are used in clinical studies in patients with chronic urticaria to evaluate efficacy of treatments, mainly antihistamine treatments, but also doxepin, cyproheptadine (7, 24), either by evaluating the proportion of patients who after treatment did not develop signs/symptoms with the cold provocation test or evaluating the response to an experimental CSTT, ie, minimum time threshold of cold stimulation required to induce a coalescent wheal and other ColdU signs and symptoms.

The ice cube provocation test is the most frequently used provocation method for ColdU in routine clinical practice and is therefore proposed for the present clinical study.

The consensus recommendations for CIndU (EAACI/GA²LEN/EDF/UNEV) (1) defines the following for provocation methods for ColdU:

- Provocation tests should be performed by applying a cold stimulus to forearm skin.
- Cold provocation testing should be performed for 5 minutes on volar forearm.
- Ice cube should be melting within a thin plastic bag to avoid cold damage of the skin and to prevent direct water contact to avoid the confusion with aquagenic urticaria if the test is positive.
- Reading time 10 minutes of rewarming after ice cube is removed.

Emergency treatment should be available at the study center to be administered by trained study center staff if severe hypersensitivity reaction occurs during the ice cube provocation test.

The ice cube provocation test procedure will be described in a separate document.

See Section 6.1.2 and Section 6.5.1 for details regarding background therapy requirements related to the ice cube provocation test and instructions how to proceed when a participant is using rescue therapy within 5 days prior to the test.

For each participant, it is recommended that the ice cube test results are read by the same study personnel during the entire study, if possible.

The primary endpoint will be the proportion of participants with negative ice cube provocation test at Week 24 compared to placebo. The negative test is defined as the absence of a confluent hive/wheal at the entire skin site of exposure after ice cube provocation test. The assessment will be done by the Investigator 10 minutes after ice cube removal. The result will be recorded in eCRF. For each ice cube provocation test room temperature and outdoor temperature should be reported in eCRF.

8.1.2 Wheal intensity Likert scale

The Wheal intensity Likert scale (ranging from 0 to 5) is a clinician-reported outcome measure comprised of a single item assessing the intensity of patients' cutaneous reaction rated as follows: 0=no wheals; 1=numerous small, noncoalescent wheals; 2= a large, regular, slightly edematous, coalescent wheal; 3=a large and moderately edematous wheal; 4=a large, regular, and significantly edematous wheal without pseudopodia; and 5=a large, very edematous wheal with pseudopodia (28, 29).

Investigators will complete the scale at the study visit, 10 minutes after removal of the ice cube from the participant's arm. Investigators will complete the wheal intensity Likert scale in eCRF as described in the SoA (Section 1.3).

8.1.3 Peak pruritus numerical rating scale (NRS), peak pain NRS, and peak burning sensation NRS

Participants will undergo a temperature provocation test using ice cube at study visits at study center. Ten minutes after the removal of the ice cube from their arm, participants will be asked to rate the severity of local itch, pain, and burning sensation at the provocation site skin using a NRS.

The peak pruritus NRS is a PRO comprised of a single item rated on a scale from 0 ("No itch") to 10 ("Worst itch imaginable"). Participants will be asked to rate the intensity of their worst local site pruritus (itch) 10 minutes after removal of the ice cube. The 24-hour version of the scale has been developed, tested and validated with patients with AD; a threshold value of 4 has been determined as a meaningful within-person change in score in adults and adolescent patients with AD (30).

The peak pain NRS is a PRO comprised of a single item rated on a scale from 0 ("No pain") to 10 ("Worst imaginable pain"). Participants will be asked to rate the intensity of their worst local site pain 10 minutes after removal of the ice cube.

The peak burning sensation NRS is a PRO comprised of a single item rated on a scale from 0 ("No burning sensation") to 10 ("Worst imaginable burning sensation"). Participants will be asked to rate the intensity of the worst local site burning sensation of their skin 10 minutes after the removal of the ice cube.

Participants will complete the NRS as described in the SoA (Section 1.3).

8.1.4 Urticaria control test (UCT) 4-item version

The UCT is a PRO questionnaire for assessing urticaria control. The questionnaire has been developed and validated with patients with CSU and CIndU (25). It is comprised of 4 items: severity of physical symptoms of urticaria (itch, hives and/or swelling); QoL impairment; frequency of treatment being not sufficient to control urticaria; overall urticarial control. Recall period is "last four weeks". Each item is rated on a 5-point Likert scale (scored with 0 to 4 points). Low scores indicate high disease activity and low disease control. The UCT total score is

calculated by adding all 4 individual item scores. Accordingly, the minimum and maximum UCT scores are 0 and 16, with a score of 16 for complete disease control (25).

The minimal important difference (MID) of the UCT is determined to be 3 (31).

Participants will complete the UCT as described in the SoA (Section 1.3).

8.1.5 Cold Urticaria Activity Score

The ColdUAS is a disease-specific PRO questionnaire designed to determine cold urticaria disease activity. ColdUAS is intended for patients with cold urticaria aged 12 years old and above; it has been developed and comprehensively tested with adults and adolescent patients with cold urticaria. Disease activity assessment is based on the daily documentation of cold-induced skin reactions (wheals and swelling), skin sensations (itching, burning, pain or feeling hot), avoidance behavior and trigger exposure, and overall symptoms severity. Skin reaction, skin sensations, exposition to cold temperatures that usually cause ColdU symptoms and overall symptom severity are rated on a 4-point scale from 0 (“No”) to 4 (“Yes, severe”); avoidance of cold temperatures that usually lead to ColdU symptoms are answered using responses “No”, “Yes partially avoided”, “Yes completely avoided”.

After each week of completion, participants will be asked 2 additional questions about the overall disease activity of their ColdU in the past week using a 4-point Likert scale from “No disease activity” to “High disease activity” and 1 question about their current disease activity in the past week compared with before treatment using a 4-point Likert scale.

Participants will complete the ColdUAS as described in the SoA (Section 1.3).

8.1.6 Dermatology Life Quality Index and Children’s Dermatology Life Quality Index

The DLQI is a PRO developed to measure dermatology-specific HRQoL in adult participants (26). The instrument comprises 10 items assessing the impact of skin disease on participant’s HRQoL over the previous week. The items cover symptoms, leisure activities, work/school or holiday time, personal relationships including intimate, the side effects of treatment, and emotional reactions to having a skin disease. It is a validated questionnaire used in clinical practice and clinical trials (32). The response scale is a 4-point Likert scale (0 = “Not at all” and 3 = “Very much”) for 9 items. The remaining 1 item about work/studying asks whether work/study has been prevented and then (if “No”) to what degree the skin condition has been a problem at work/study; the item is rated on a 3-point Likert scale (“Not at all” to “A lot”). Overall scoring ranges from 0 to 30, with a high score indicative of a poor HRQoL. Using an integrated analysis of distribution and anchor-based approaches using the change in DLQI total score and participant-assessed itch severity scores, the MID for the DLQI in participants with chronic idiopathic urticaria was reported to be in the range of 2.24 to 3.10 points (33). So far, there is no MID value determined for chronic inducible ColdU patients.

The CDLQI is a validated questionnaire designed to measure the impact of skin disease on children’s HRQoL (34). Participants provide responses to 10 questions (symptoms feelings associated with disease, the impact of the disease on leisure, school or holidays, personal

relationships, sleep, and side effects of treatment for the skin disease). The instrument has a recall period of 7 days. Nine of the 10 questions are scored on a 4-point Likert scale ranging from 0=Not at all/question unanswered to 3=Very much. Question 7 has an additional possible response (prevented school), which is assigned a score of 3. The CDLQI total score is the sum of the score of each question with a maximum of 30 and a minimum of 0. The higher the score, the greater the impact is on the child's HRQoL.

Participants will complete the DLQI (≥16 years old) or CDLQI (≥12 to <16 years old) as described in the SoA (Section 1.3).

8.1.7 Cold Urticaria Quality of Life Questionnaire

The ColdU-QoL questionnaire is a newly developed disease-specific PRO questionnaire designed to assess the impact of cold urticaria on patients' HRQoL. It has been developed and comprehensively tested with adults and adolescent patients with cold urticaria. The questionnaire contains 19 items, each rated using 5-point Likert scale from 0 (Not at all / Never) to 4 (Very much / Very often), with a "Last 2 weeks" recall period. The total raw score of the ColdU-QoL is transformed to a 0-100 scale with higher scores indicating higher ColdU-related QoL impairment.

Participants will complete the ColdU-QoL as described in the SoA (Section 1.3)

8.1.8 Patient Global Impression of Change of chronic inducible ColdU disease and Patient Global Impression of Severity of chronic inducible ColdU disease

The PGIC is a 1-item questionnaire that asks the participant to provide the overall self-assessment of change in their chronic inducible ColdU on a 7-point scale, compared with just before participant started taking the study treatment. Response choices are: 0="Very much better", 1="Moderately better", 2="A little better", 3="No change", 4="A little worse", 5="Moderately worse", 6="Very much worse".

The PGIS is a 1-item questionnaire that asks participants to provide the overall self-assessment of their chronic inducible ColdU current severity on a 4-point scale. Response choices are: 1="None", 2="Mild", 3="Moderate", 4="Severe".

Participants will complete the 2 items after having answered the peak pruritus NRS, pain NRS, and skin burning sensation NRS as described in the SoA (Section 1.3).

8.1.9 Acquired Cold Urticaria Severity Index

The Acquired Cold Urticaria Severity Index (ACUSI) is a measure designed to evaluate the severity of the ACU signs/symptoms (35). It is composed of 4 questions regarding the severity of ACU: 1) worst problems ever caused by cold urticarial; 2) season during which problems with outdoor activities occur because it was too cold; 3) maximum treatment needed; 4) frequency of complains. Questions 1, 3, and 4 are attributed 1 to 4 points, and question 3 is attributed 1 to 3 points, thus resulting in a score ranging from 4 to 15. Scores of 4 to 7, 8 to 11, and 12 to

15 points indicate low, middle, and high ACU severity, respectively. A fifth question assesses the overall severity of the disease between mild, moderate, and severe.

The ACUSI questionnaire will be administered during the screening period and will be captured in the eCRF.

8.1.10 EuroQol-5 Dimensions questionnaire

The EuroQol-5 dimensions (EQ-5D) is a standardized PRO measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D consists of 2 parts: the descriptive system and the EuroQol visual analogue scale (EQ-VAS). The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels of perceived problems: “no problem”, “slight problems”, “moderate problems”, “severe problems”, and “extreme problems” (36). The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions; this results in a 1-digit number expressing the level for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent’s health state. The EQ-VAS records the respondent’s self-rated health on a vertical, visual analogue scale where the endpoints are labeled “best imaginable health state (100)” and “worst imaginable health state (0)”. This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

The recall period is “today”.

Participants will complete the questionnaire as described in the SoA (Section 1.3).

8.1.11 Health care resource utilization/productivity

A questionnaire on health care resource utilization and productivity (missed days of school [12 to 17 years old]/workdays [18 and above]) will be collected by the Investigator for all participants throughout the study through eCRF.

Participants will complete the questionnaire as described in the SoA (Section 1.3).

8.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical examinations

- A complete physical examination will include skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

- Any new finding or worsening of previous finding should be reported as a new AE.

8.2.2 Vital signs

- Vital signs will be measured in a semi-supine or sitting position after 5 minutes rest and will include axillary or oral temperature (same method of temperature measurement should be used during the course of the study), systolic and diastolic blood pressure, and pulse and respiratory rate. Blood pressure and pulse measurements should be assessed using the same arm with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Body weight (kg) will be measured at screening (Visit 1) and at EOT/EOS Visits. Height will be measured at screening visit (Visit 1). Height and weight should be measured with indoor clothing but without shoes.

8.2.3 Electrocardiograms

- A single standard 12-lead ECG will be obtained at the screening visit (Visit 1) as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. The ECG should be recorded after 10 minutes of rest in the supine position. The ECG will be read locally and results reported in the eCRF. In case of a clinically significant finding the Investigator should assess if it impacts a participant's eligibility and document this in the medical records. An AE should be reported if appropriate.

8.2.4 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests including pregnancy testing to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.
- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3).

An AE will be reported by the participant (or, when appropriate, by a caregiver, parent, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs, serious or nonserious, will be collected from the signing of the ICF until the EOS Visit at the time points specified in the SoA (Section 1.3).

All SAEs and AESIs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE/AESI data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end date, all SAEs, and non-serious AESIs (as defined in Section 8.3), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Adverse events that are considered expected will be specified in the reference safety information.
- Suspected unexpected serious adverse reactions (SUSAR) are reported to regulatory authorities, Investigators, and IRBs/IECs as follows:
  - For SUSARs that are life-threatening or result in death, reporting is no later than 7 days after first knowledge by the Sponsor, with all relevant follow-up information subsequently reported within an additional 8 days
  - For SUSARs, other than those that are life-threatening or result in death, reporting is no later than 15 days after first knowledge by the Sponsor.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR, or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities. IB is reference safety information for considering AEs as expected.

8.3.5 Pregnancy

- Details of all pregnancies in female participants will be collected from the signing of the ICF up to the EOS Visit or within 12 weeks after last study intervention, whichever was later. Details of all pregnancies in female partners of male participants will be collected after the start of study intervention up to the EOS Visit or within 12 weeks after last study intervention, whichever was later.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4). The IMP should be permanently discontinued in case of pregnancy of female participant (see Section 7.1.1).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

An episode of ColdU should be reported as an AE or SAE only if judged by the Investigator to have unexpectedly worsened in severity and/or frequency or change in nature any time during the study. If the participant has a preexisting medical history of angioedema and this condition worsens during the study, it should be reported as an AE or SAE. Any new onset of angioedema in the participant with no prior occurrence should also be reported as an AE or SAE.

Any other AE not listed as an expected event in the IB or in this protocol will be considered unexpected.

8.3.7 Adverse event of special interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified, or removed during a study by protocol amendment.

- Anaphylactic reactions
- Systemic hypersensitivity reactions
- Helminthic infections
- Any severe type of conjunctivitis or blepharitis
- Keratitis
- Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)
- Significant ALT elevation
  - ALT >5 × the ULN in participants with baseline ALT ≤2 × ULN;

  or
  - ALT >8 × ULN if baseline ALT >2 × ULN.
- 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.
  - Pregnancy occurring in a female participant entered in the clinical study or in a female partner of a male participant entered in the clinical study. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (See Appendix 4 [Section 10.4])
- Symptomatic overdose (serious or nonserious) with IMP/Noninvestigational medicinal product (NIMP)

- An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and defined as at least twice the intended dose during an interval of less than 11 days. The circumstances (ie, accidental or intentional) should be clearly specified in the overdose form. An overdose (accidental or intentional) with any NIMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and defined as at least twice the maximum prescribed daily dose, within the intended therapeutic interval. The circumstances (ie, accidental or intentional) should be clearly specified in the overdose form.

8.3.7.1 Anaphylactic reactions

A serious feature of ColdU is anaphylaxis. Thirty-five percent to 70% of patients with chronic inducible ColdU have experienced systemic reactions including anaphylaxis in severe cases. (6, 37, 38).

Anaphylaxis is defined as a severe, potentially life-threatening systemic hypersensitivity reaction, characterized by being rapid in onset with life-threatening airway, breathing, or circulatory problems that is usually, though not always, associated with skin and mucosal changes.

When the diagnosis of anaphylaxis is made, the basis for having suspected the diagnosis must be documented, using the criteria in Appendix 10 (Section 10.10), established by the Second Symposium on the Definition and Management of Anaphylaxis (37, 39). Reports of anaphylaxis will be collected as AESIs in the eCRF.

All participants with ColdU and their parents/legal representative/caregiver should be cautioned regarding the risk of anaphylaxis and provided with an epinephrine autoinjector.

The proportion of participants with cold exposure triggered urticaria requiring emergency medical care visit or treatment with epinephrine (after provocation test and/or at home) will be evaluated.

8.3.8 Guidelines for reporting product complaints

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team who will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.4 TREATMENT OF OVERDOSE

Symptomatic overdose (serious or nonserious) with IMP/NIMP is considered as an AESI (defined in Section 8.3.7). No antidote is available for dupilumab. The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator/treating physician should:

1. Contact the Sponsor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until dupilumab can no longer be detected systemically (at least 98 days).
3. Obtain a plasma sample for PK analysis as soon as possible from the date of the last dose of IMP if requested by the Sponsor (determined on a case-by-case basis).
4. Document appropriately in the eCRF.

Decisions regarding dose interruptions will be made by the Investigator in consultation with the Sponsor based on the clinical evaluation of the participant.

8.5 PHARMACOKINETICS AND IMMUNOGENICITY ASSESSMENTS

8.5.1 Systemic drug concentration and antidrug antibodies

8.5.1.1 Sampling time

Blood samples will be collected for determination of functional dupilumab and anti-dupilumab antibodies in serum as specified in the SoA (Section 1.3). Special procedures for the collection, storage, and shipping of serum are described in separate operational manuals. The date of collection should be recorded in the eCRF.

8.5.1.2 Handling procedures

Special procedures for collection, storage, and shipping of serum are described in separate operational manuals. An overview of the handling procedure for samples used in the determination of systemic drug concentration and antidrug antibodies (ADA) is provided in Table 4.

Table 4 - Summary of handling procedures

Sample type	Functional dupilumab	Anti-dupilumab antibody
[redacted]		

8.5.1.3 Bioanalytic method

Serum PK and ADA samples will be assayed using validated methods as described in Table 5.

Table 5 - Summary of bioanalytical methods for functional dupilumab and anti-dupilumab antibodies

Analyte	Functional dupilumab	Anti-dupilumab antibody
[redacted]		

Note: In the event of any SAE, any AE of severe injection site reaction lasting longer than 24 hours, or any AESI of anaphylactic reaction or systemic allergic reaction that is related to IMP and requires treatment, PK and ADA samples will be collected at or near the onset of the event for any additional analysis if required or for archival purposes. The exact date and time of sample collection must be recorded and entered into the database by the central laboratory. An unscheduled systemic drug concentration page in the eCRF must be completed as well. If necessary for safety monitoring, additional PK and ADA samples may be collected after the EOS Visit until resolution of the AE.

8.6 PHARMACODYNAMICS

See Section 8.8 for IgE measurement. No other PD parameters will be evaluated in this study.

8.7 GENETICS

For those participants who consent to the optional pharmacogenetic/pharmacogenomic sample collection section of the ICF, blood samples for exploratory genetic analysis of DNA or RNA will be collected and stored for possible future use, including sequencing. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

Details on processes for collection and shipment and destruction of these samples can be found in the laboratory manual.

8.8 BIOMARKERS

Collection of samples for biomarker research is also part of this study.

As specified in the SoA, venous blood samples will be collected from all participants for measurement of total serum IgE, which will be done using a validated quantitative method.

Optional samples for biomarker research that should be collected from participants in the study where possible are the following:

- Serum and plasma:
  - Samples will be collected and stored for possible future analysis of potential biomarkers of drug response, disease activity, safety, and type 2 inflammation. See Section 8.8.1
- Basophil activation test (substudy)
  - Blood will be collected at selected sites for assessment of basophil activation using a validated assay.

Adolescents will not participate in the optional assessments. See SoA for additional details.

In addition, for participant(s) who have consented to it, samples that are unused or left over after planned testing may be used for additional research purposes, including developing assay methods, possible analysis of potential biomarkers of drug response, disease activity, safety, and type 2 inflammation, and developing companion diagnostics.

8.8.1 Use of Biological Samples and Data for Future Research

Future research may help further the understanding of disease subtypes, disease biology, related conditions, drug response and toxicity, and can help identify new drug targets or biomarkers that predict participant response to treatment. Therefore, data and biological samples will be stored and used for future research when consented to by participants (see Section 10.1.3) unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of sample will not be included in the local ICF).

For participants who consent to the storage and use of their data and remaining and/or extra clinical samples, data and samples may be used after the study ends for future research related either to the drug, the mechanism of action, and the disease or its associated conditions. Such research may include, but is not limited to, performing assessments on DNA, RNA, proteins or metabolites. If future research on genetic material is performed, this will also be limited to the purpose of addressing research questions related to the drug, the mechanism of action, the disease or its associated conditions.

In the event future research is conducted for other purposes, the study participants will be informed of those purposes and will be given means to object to those research projects.

Data and samples will be used in compliance with the information provided to participants in the ICF Part 2 (future research).

All study participant data and samples will be coded such that no participant direct identifiers will be linked to them. Coded data and samples may be transferred to a Sponsor site (or a subcontractor site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

The samples will be stored for a maximum of 15 years after the end of the study (or according to local regulations). Any samples remaining at the end of retention period will be destroyed. If a

participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.

Study participant coded data will be stored for future research for up to 25 years after the end of the study. If data are still considered of important scientific value after this period, coded data already available will be anonymized unless otherwise required by applicable laws (the same will apply to the data of a study participant who has requested the destruction of his/her samples).

Participant's coded data sets provided to researchers for a specific research project will be available to the researchers for a maximum of 2 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

8.9 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

A questionnaire on health care resource utilization and productivity will be used in this study. Number of missed school/workdays collection is described in Section 8.1.11

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The statistical hypothesis for comparing dupilumab against placebo for the primary endpoint of the proportion of participants with negative ice cube provocation test at Week 24 is:

- Null hypothesis H0: No treatment difference between dupilumab and placebo.
- Alternative hypothesis H1: There is a treatment difference between dupilumab and placebo.

The statistical hypotheses to be tested on the secondary endpoints can be specified similarly.

9.2 SAMPLE SIZE DETERMINATION

To adequately power the study for the comparison of the primary endpoint of the proportion of participants with negative ice cube provocation test at Week 24 between the 2 groups, the sample size was calculated based on the following assumptions:

1. The placebo group has [redacted] of participants with negative ice cube provocation test at Week 24 and the dupilumab group has [redacted] 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 randomized to the dupilumab group and the placebo group.

With these assumptions, 39 participants per group (78 participants in total) will provide 90% power to detect the difference of [redacted] response rate in the dupilumab group and [redacted] response rate in the placebo group. The sample size calculations were performed using nQuery+nTerim 4.0.

9.3 POPULATIONS FOR ANALYSES

The analysis populations are defined in Table 6.

Table 6 - Analyses population

Population	Description
Screened	All participants who sign the ICF
Randomized	The randomized population includes all participants with a treatment kit number allocated and recorded in the IRT database, and 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 treatment group allocated by randomization.
Efficacy	The ITT population
Safety	All participants randomly assigned to IMP and who take at least 1 dose of study IMP. Participants will be analyzed according to the intervention they actually received. Randomized participants for whom it is unclear whether they took the study IMP will be included in the safety population as randomized. For participants who accidentally receive different treatment from the planned, the actual intervention allocation for as-treated analysis will be the dupilumab group. The PD analyses will be performed on the safety population.
Pharmacokinetic (PK)	The PK population includes all participants in the safety population with at least 1 non-missing result for functional dupilumab concentration in serum after first dose of the IMP. Participants will be analyzed according to the intervention actually received.
Antidrug antibody (ADA)	ADA population includes all participants in the safety population who have at least 1 non-missing ADA result after first dose of the IMP. Participants will be analyzed according to the intervention actually received.

Abbreviations: ADA = antidrug antibody; ICF = Informed consent form, IMP = investigational medicinal product; IRT = Interactive response technology; ITT = intent-to-treat; PD = Pharmacodynamic; PK = Pharmacokinetic.

9.4 STATISTICAL ANALYSES

The SAP will be finalized prior to database lock and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and the key secondary endpoints.

9.4.1 Efficacy analyses

Statistical analysis methods for the primary, secondary, and tertiary/exploratory endpoints are presented in the table below (Table 7). In addition, for the primary and secondary endpoints, the primary estimand and details about the intercurrent events strategy and missing data handling are presented in Appendix 13 (Section 10.13).

Table 7 - Efficacy analyses

Endpoint	Statistical analysis methods
Primary Primary endpoint: Proportion of participants with negative ice cube provocation test at Week 24	The primary efficacy endpoint will be analyzed using the Cochran-Mantel-Haenszel test stratified by region 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 will be derived and the corresponding odd ratios and the 95% confidence interval (CI) will be reported. Participants who receive highly influential prohibited medications and/or highly influential rescue medications (details of selection will be specified in the statistical analysis plan [SAP]) will be considered as having positive ice cube provocation tests for time points after the medication usage. For other participants, all available data including those collected during the off-treatment period will be used to determine the positive/negative ice cube provocation test outcome. Participants with missing ice cube provocation test data at Week 24 will be considered as having positive ice cube provocation tests. Sensitivity analysis Tipping point analyses and other sensitivity analyses will be performed to confirm robustness of the results with respect to the missing data handling. Details of the sensitivity analyses will be provided in the SAP. Subgroup analysis To assess the consistency in treatment effects across different subgroup levels, subgroup analyses will be performed for the primary efficacy endpoint with respect to age group, gender, region, and other factors that will be specified in the SAP.
Secondary • 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) • 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) • 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) • 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) • Change from baseline in urticaria control test (UCT 4-item) at Week 24	The secondary endpoints at Week 24 will be analyzed using analysis of covariance (ANCOVA) with multiple imputation. For participants taking highly influential prohibited medications and/or highly influential rescue medications (details of selection will be specified in the SAP), their data after the medication usage will be set to missing, and the WOCF approach (worst postbaseline observation for the participant will be carried forward) will be used to impute missing Week 24 value (for participants whose postbaseline values are all missing, the participant's baseline value will be used to impute the missing endpoint value). Participants who discontinue the treatment prematurely are encouraged to follow the planned clinical visits. For participants who did not take the highly influential prohibited medications and/or highly influential rescue medications, all data collected after treatment discontinuation will be used in the analysis. For these participants, missing data may still happen despite all efforts have been tried to collect the data after treatment discontinuation. For participants who discontinue study intervention due to lack of efficacy, all data collected after discontinuation will be used in the analysis, and a WOCF approach will be used to impute missing Week 24 value if needed. For participants who discontinue study intervention not due to lack of efficacy, a multiple imputation approach will be used to impute missing Week 24 value, and this multiple imputation will use all

Endpoint	Statistical analysis methods
• Change from baseline in cold urticaria signs and symptoms severity at Week 24 on cold exposure days as measured by ColdUAS • 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 • 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 • Change from baseline in Cold Urticaria Quality of Life (ColdU-QoL) at Week 24.	participants excluding participants who have taken the highly influential prohibited medications and/or highly influential rescue medications on or before Week 24 and excluding patients who discontinue due to lack of efficacy on or before Week 24. Each of the imputed complete data will be analyzed by fitting an analysis of covariance model with the baseline value of the endpoint, treatment group, region (combined countries), and background H1-antihistamine regular/daily use (Yes/No) as covariates. Statistical inference obtained from all imputed data will be combined using Rubin's rule. Descriptive statistics including number of participants, mean, standard error, and least squares (LS) mean changes (and standard error) score will be provided. In addition, difference of the dupilumab group against placebo in LS means and the corresponding 95% CI will be provided along with the p-values. The continuous endpoints at Week 12 will be analyzed in a similar way as the secondary endpoints at Week 24. Detailed analyses will be described in the SAP finalized before database lock.
Secondary • Proportion of participants with negative ice cube provocation test at Week 12 • Proportion of well-controlled participants (UCT ≥12) at Week 24 • Proportion of participants with an improvement of ≥3 in UCT 4- item from baseline to Week 24	These binary endpoints will be analyzed in a similar way as the primary endpoint.
Secondary • Proportion of participants receiving rescue therapy for chronic induced ColdU during the planned treatment period • Proportion of participants with cold exposure triggered urticaria requiring emergency medical care visit or treatment with epinephrine (at provocation test and/or at home)	These binary endpoints will be summarized using the count and percentage of participants.
Tertiary/Exploratory • [redacted] • [redacted] • [redacted]	

Endpoint	Statistical analysis methods
• [redacted] • •	

A multiplicity hierarchical testing will be proposed to control the overall Type-I error rate for testing the primary endpoint, selected PRO(s), and the other key secondary endpoints. The study is considered positive when the primary endpoint achieves statistical significance. A detailed multiplicity adjustment procedure for the efficacy endpoints will be described in the study SAP.

9.4.2 Safety analyses

All safety analyses will be performed on the safety population (Table 8). The summary of safety results will be presented by treatment group. The baseline value is defined generally as the last available value before randomization.

Table 8 - Safety analyses

Endpoint	Statistical Analysis Methods
AE, SAE, AE leading to death, AE leading to permanent treatment discontinuation	Adverse event incidence tables will present by system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high-level term (HLT) and preferred term (PT) sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of participants experiencing an AE. Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group. Proportion of participants with at least 1 treatment-emergent adverse event (TEAE), treatment-emergent SAE, TEAE leading to death, and TEAE leading to permanent treatment discontinuation will be tabulated by treatment group. In addition, TEAEs will be described according to maximum intensity and relation to the IMP. Serious AEs and AEs leading to study discontinuation that occur outside the treatment-emergent period will be summarized separately.
AESI and other AE groupings	Incidence of each type of AESI and other AE groupings will be tabulated by treatment group. For each type of AESI, the following analysis will be generated. • A summary of the number (%) of participants with - Any TEAE. - Any SAE (regardless of treatment-emergent status). - Any treatment-emergent SAE. - Any AE leading to death. - Any TEAE leading to permanent treatment discontinuation. - Any TEAE related to study intervention reported by the Investigator. - Any TEAE by maximum intensity, corrective treatment, and final outcome. • Kaplan-Meier (K-M) estimates of probability of having at least one TEAE at specific time points, and K-M curve to depict the course of event onset over time. The method to identify AESIs and other AE groupings will be specified in the SAP.
Death	The following deaths summaries will be generated: • Number (%) of participants who died during the study period (TEAE, on-study) summarized on the safety population by treatment received. • Death in nonrandomized participants or randomized and not treated participants. • TEAE leading to death (death as an outcome on the AE eCRF page as reported by the Investigator) by primary SOC, HLGT, HLT, and PT showing number (%) of participants sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.
Laboratory parameters	Results and change from baseline for the parameters will be summarized by treatment group for baseline and each postbaseline time point, endpoint, and minimum and maximum value. Summary statistics will include number of participants, mean, standard deviation, median, Q1, Q3, minimum, and maximum. The following definitions will be applied to laboratory parameters. • The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests. • PCSA criteria will determine which participants had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including unscheduled or repeated evaluations. The number of all such participants will be the numerator for the on-treatment PCSA percentage.

Endpoint	Statistical Analysis Methods
	The proportion of participants who had at least 1 incidence of PCSA at any time during the treatment-emergent period will be summarized by treatment group. Shift tables showing changes with respect to the baseline status will be provided.

Abbreviations: AE = adverse event; AESI = adverse events of special interest; eCRF = electronic case report form; IMP = investigational medicinal product; SAE = serious adverse event; SAP = statistical analysis plan.

9.4.3 Other analyses

Pharmacokinetic, immunogenicity, PD, and biomarker exploratory analyses will be described in the SAP finalized before database lock. The population PK and PD analyses might be presented separately from the main CSR.

Data collected regarding the impact of the COVID-19 or other pandemics on the participants will be summarized (eg, discontinuation due to COVID-19). Any additional analyses and methods that might be required to investigate the impact of COVID-19, or other pandemics declared as a public health emergency on the efficacy (eg; missing data due to COVID-19) and safety will be detailed in the SAP.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

9.5 INTERIM ANALYSES

No interim analysis is planned for this study.

A primary database lock will be performed when all randomized participants have completed their treatment phase. Final analyses in the CSR will be based on all data collected up to this database lock.

The database will be updated at the end of the study for all participants to include the post-treatment follow-up information and updates for the events previously ongoing at the time of the primary lock. Additional data between this database lock and last participant completing last visit will be summarized in a CSR addendum.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH-GCP Guidelines
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation [GDPR])
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the study center and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participant (and the parent of adolescent) or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants (and parents of adolescents) or legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center. Adolescents will sign simplified informed consent. If during the study the adolescent reaches the age of majority he/she needs to re-consent.
- The medical record must include a statement that written informed consent was obtained before the participant was randomized in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

The ICF contains 2 separate sections that addresses the use for research of participants' data and/or samples (remaining mandatory ones or new extra samples collected for optional research). Optional exploratory research must be detailed in the section "Optional tests/procedures" and future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2. Each option is subject to an independent consent and must be confirmed by ticking a checkbox in CSICF Part 3. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research and why data and samples are important for future research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. Please note that adolescents will not participate to optional exploratory research.

For adults only, the ICF will also contain a separate section concerning the other optional tests (genetic testing [DNA/RNA sampling], and basophil activation test). A separate signature for each optional test will be required to document a participant's agreement to this. Participants who decline to participate in this optional test will not provide this separate signature.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9)

10.1.4 Data protection

All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all

applicable laws and regulations including the GDPR. The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

"Participant race and ethnicity will be collected in this study because these data are required by regulatory agencies (eg, on afro American population for the Food and Drug Administration or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan)". They will not be collected in the countries where this is prohibited by local regulation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.
- When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation[s] details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.

- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
  - Sanofi's Binding Corporate Rules for intra-group transfers.
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to 30 years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committees structure

There will be no study committees.

10.1.6 Dissemination of clinical study data

Study participants

Sanofi shares information about clinical studies and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical studies in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to https://vivli.org.

Individual participant data and supporting clinical documents are available for request at https://vivli.org. While making information available we continue to protect the privacy of participants in our clinical studies. Details on data sharing criteria and process for requesting access can be found at this web address: https://vivli.org.

Professionals involved in the study or in the drug development program

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "European Federation of Pharmaceutical Industries and Associations (EFPIA) Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organizations".

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF completion instructions.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations)
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized study center personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9 Study and study center closure

The Sponsor or designee reserves the right to close the study center or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study centers will be closed upon study completion. A study center is considered closed when all required documents and study supplies have been collected and a study center closure visit has been performed.

The Investigator may initiate study center closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study termination by the Sponsor, as well as reasons for the early closure of a study center by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio.
  - Discontinuation of further study intervention development.
- For study center termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
  - Total number of participants included earlier than expected.

10.1.10 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual study center data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

The tests detailed in Table 9 will be performed by the central laboratory. The participants do not need to be fasting for blood sampling.

- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 9 - Protocol-required laboratory assessments

Laboratory assessments	Parameters
Hematology	
	Platelet count
	Red blood cell count
	Hemoglobin
	Hematocrit
	White blood cell count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Clinical chemistry[a]	
	Blood urea nitrogen
	Creatinine
	Glucose
	Lactate dehydrogenase
	Uric acid
	Total cholesterol
	Albumin
	Potassium
	Sodium
	Chloride
	Bicarbonate
	Creatine Phosphokinase
	Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic transaminase
	Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase
	Alkaline phosphatase

Laboratory assessments	Parameters
	Total bilirubin Total protein
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, (bilirubin, urobilinogen, nitrite, leukocyte esterase) by dipstick • Microscopic examination (if blood or protein is abnormal)
Other screening tests	• For women of childbearing potential: serum pregnancy test at screening visit (Visit 1) and urine pregnancy tests at baseline visit (Visit 2) and every 4 weeks during the study. A negative result must be obtained at Visit 1 and at Visit 2 prior to randomization. In case of positive urine test the study treatment will be withheld and a serum pregnancy test to confirm the pregnancy should be performed as soon as possible. Pregnancy testing should be done monthly, female participants will be supplied with dipsticks for months with no study center visits planned. For the urine pregnancy tests performed at home female participants will have to complete a pregnancy test diary. In female participants who discontinue the study intervention the pregnancy testing should continue for minimum of 12 weeks after the last dose of study intervention. • Hepatitis serologic testing at screening visit (Visit 1): hepatitis B surface antigen (HBs Ag), hepatitis B surface antibody (HBs Ab), hepatitis B core antibody (HBc Ab), and hepatitis C virus antibodies (HCV Ab). In case of results showing HBs Ag (negative) and HBc Ab (positive), an HBV DNA testing will be performed and should be confirmed negative prior to randomization. In case of results showing HCV Ab (positive), an HCV RNA testing will be performed and should be confirmed negative prior to randomization. • Human Immunodeficiency Virus (HIV) serologic testing at screening visit (Visit 1): HIV screen (Anti-HIV-1 and HIV-2 antibodies). • Tuberculosis test (to be performed locally if required). The results of each test must be entered into the eCRF.

Abbreviations: DNA = deoxyribonucleic acid; eCRF = electronic case report form; HBV = hepatitis B virus, IEC = Institutional Ethics Committee; IRB = Institutional Review Board; RNA = ribonucleic acid; SAE = serious adverse event; ULN = Upper Limit of Normal.

NOTES :

a Details of liver chemistry stopping criteria with suggested actions and follow-up assessments related to liver monitoring are given in Section 7.1 and Section 10.6. All events which may indicate severe liver injury (possible Hy's Law, ALT or AST >3 × ULN and total bilirubin >2 × ULN) must be reported as an SAE.

b Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

10.3 APPENDIX 3: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a) Results in death

b) Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:
        - Intensive treatment in an emergency room or at home for:
            - Allergic bronchospasm
            - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc)
            - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
        - Development of drug dependence or drug abuse
        - ALT >3 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × ULN
        - Suicide attempt or any event suggestive of suicidality
        - Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
        - Bullous cutaneous eruptions
        - Cancers diagnosed during the study
        - Chronic neurodegenerative diseases diagnosed during the study.

10.3.3 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Sponsor's representative in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Sponsor's representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as “serious” when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor’s representative. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology, if available.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the study center will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The study center will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given study center, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a study center receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the study center can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in the protocol.

SAE reporting to the Sponsor via paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the protocol.

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

     For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the study center's personnel: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 consecutive months without an alternative medical cause.
     - Females on hormone replacement therapy (HRT)and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study

CONTRACEPTION GUIDANCE:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described below.

Table 10 - Methods of contraception

• CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
• **Highly Effective Methods[b] That Have Low User Dependency** Failure rate of <1% per year when used consistently and correctly.
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation
• Intrauterine device
• Intrauterine hormone-releasing system
• Bilateral tubal occlusion
• Vasectomized partner • (Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)
• **Highly Effective Methods[b] That Are User Dependent** Failure rate of <1% per year when used consistently and correctly.
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation - oral - intravaginal - transdermal - injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation - oral - injectable
• Sexual abstinence • (Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. *b* Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction)

COLLECTION OF PREGNANCY INFORMATION:

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue the study intervention.

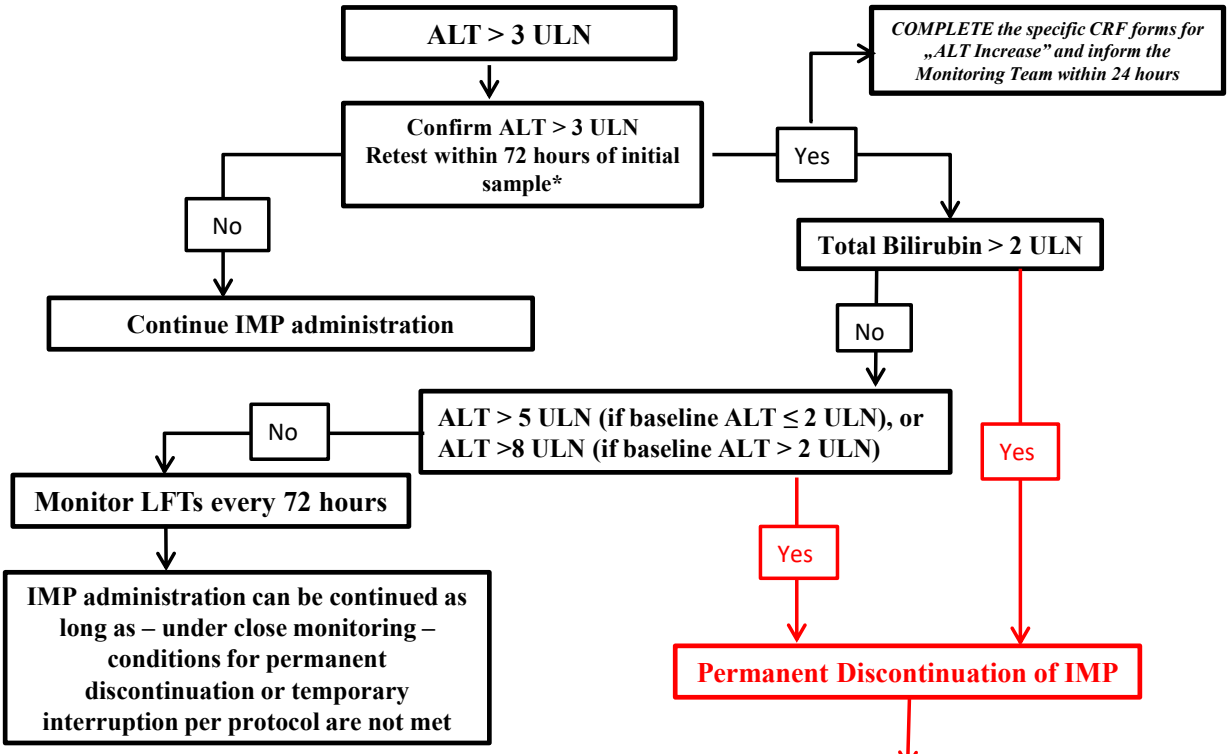
10.5 APPENDIX 5: GENETICS

Use/Analysis of DNA and RNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; safety, mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, blood samples will be collected for DNA and RNA analysis from consenting participants.
- Deoxyribonucleic acid (DNA) and RNA samples will be used for research related to dupilumab or CIndU and related diseases. They may also be used to develop tests/assays including diagnostic tests related to dupilumab or related drugs and atopic/allergic diseases. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome (including whole-exome sequencing, whole-genome sequencing, and DNA copy number variation). Transcriptome sequencing (or other methods for quantitating RNA expression) may also be performed. The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study intervention or study interventions of this class to understand study disease or related conditions.
- The Sponsor will store the DNA and RNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on study intervention or study interventions of this class or indication continues but no longer than 15 years or other period as per local requirements.

10.6 APPENDIX 6: LIVER AND OTHER SAFETY: ACTIONS AND FOLLOW-UP ASSESSMENTS

INCREASE IN ALT



In ANY CASE, FOLLOW the instructions listed in the box below:

1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
3. **PERFORM** the following tests:
   - LFTs: AST, ALT, alkaline phosphatase, total and conjugated bilirubin and prothrombin time / INR
   - CPK, serum creatinine, complete blood count
   - Anti-HAV IgM, anti-HBc IgM (HBV-DNA if clinically indicated), anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies
   - Depending on the clinical context, check for recent infection with EBV, herpes viruses, and toxoplasma
   - Hepatobiliary ultrasonography (or other imaging investigations if needed)
4. **CONSIDER** Auto-antibodies: antinuclear, anti-DNA, anti-smooth muscle, anti-LKM
5. **CONSIDER** consulting with hepatologist
6. **CONSIDER** patient hospitalisation if INR>2 (or PT<50%) and/or central nervous system disburbances suggesting hepatic encephalopathy
7. **MONITOR LFTs after discontinuation of IMP:**
   - As *closely as possible* (or **every 48 hours)** until stabilization, then every 2 weeks until return to normal/baseline or clinical resolution.
8. **FREEZE** serum sample (5ml x 2)
9. **In case of SUSPICION of GILBERT Syndrome,** a DNA diagnostic test should be done

*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.

Note:

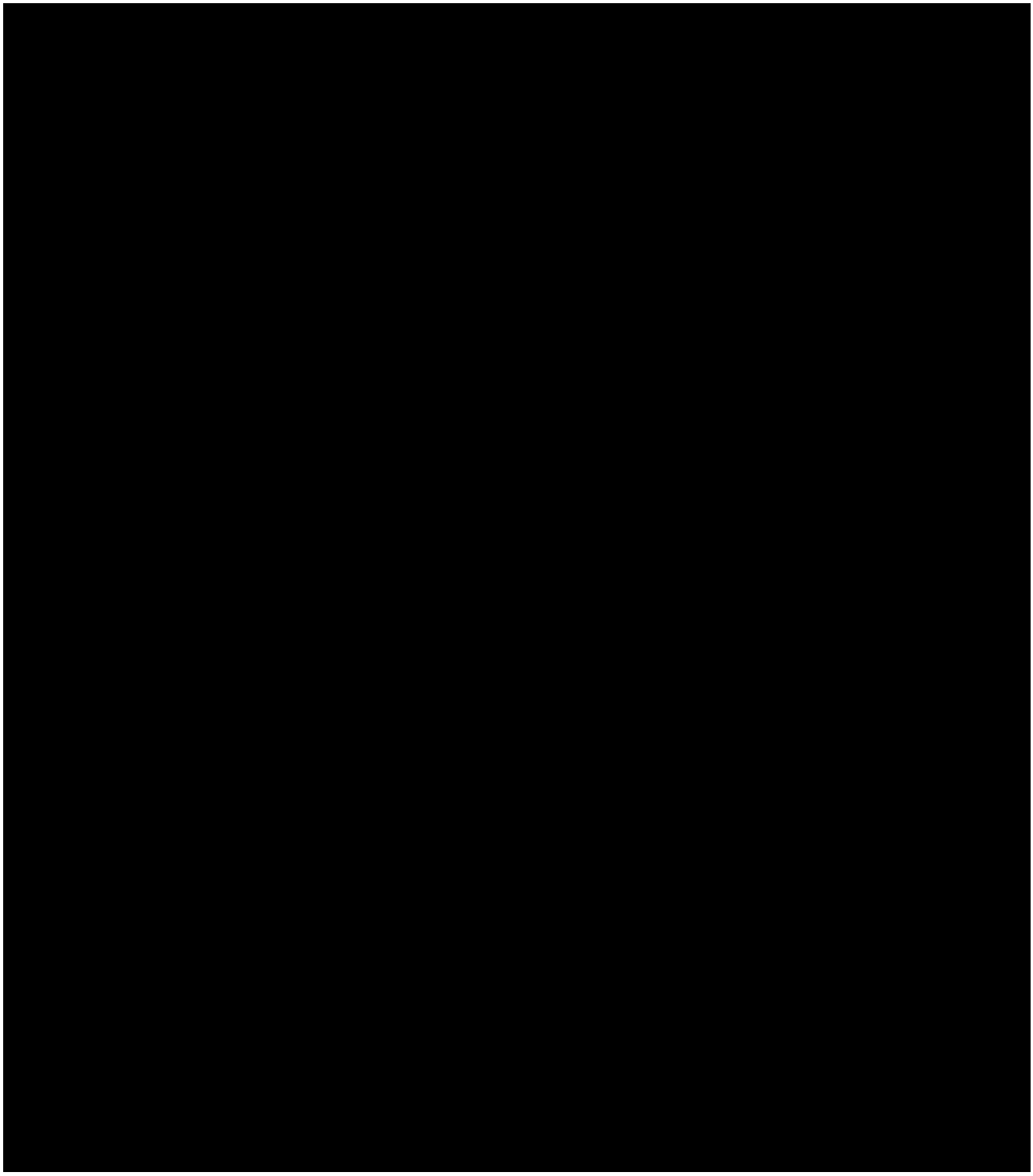
"Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.

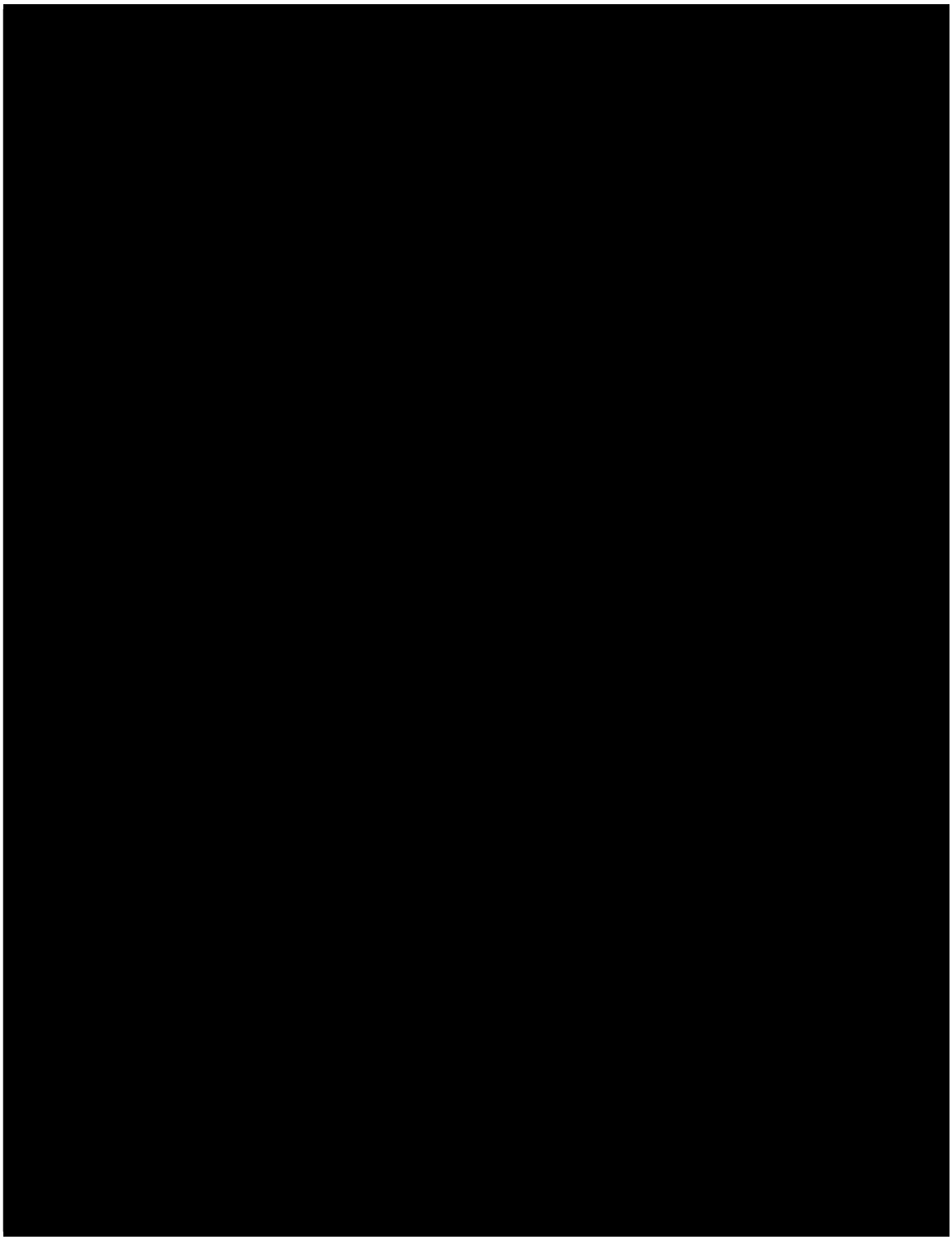
See Section 10.3 for guidance on safety reporting.

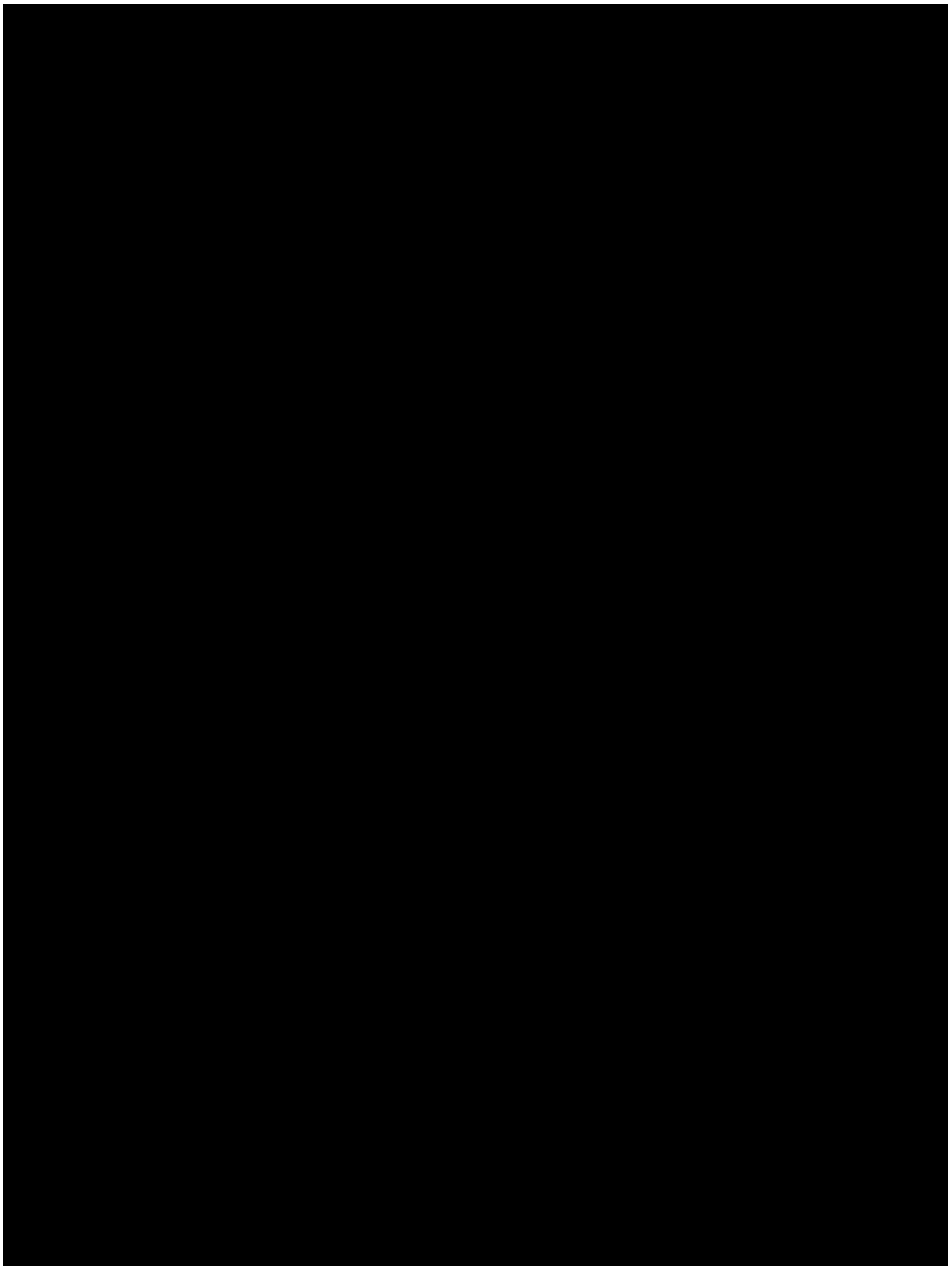
Normalization is defined as ≤ULN or baseline value, if baseline value is >ULN.

10.7 APPENDIX 7: CLINICAL-REPORTED OUTCOMES AND PATIENT-REPORTED OUTCOMES

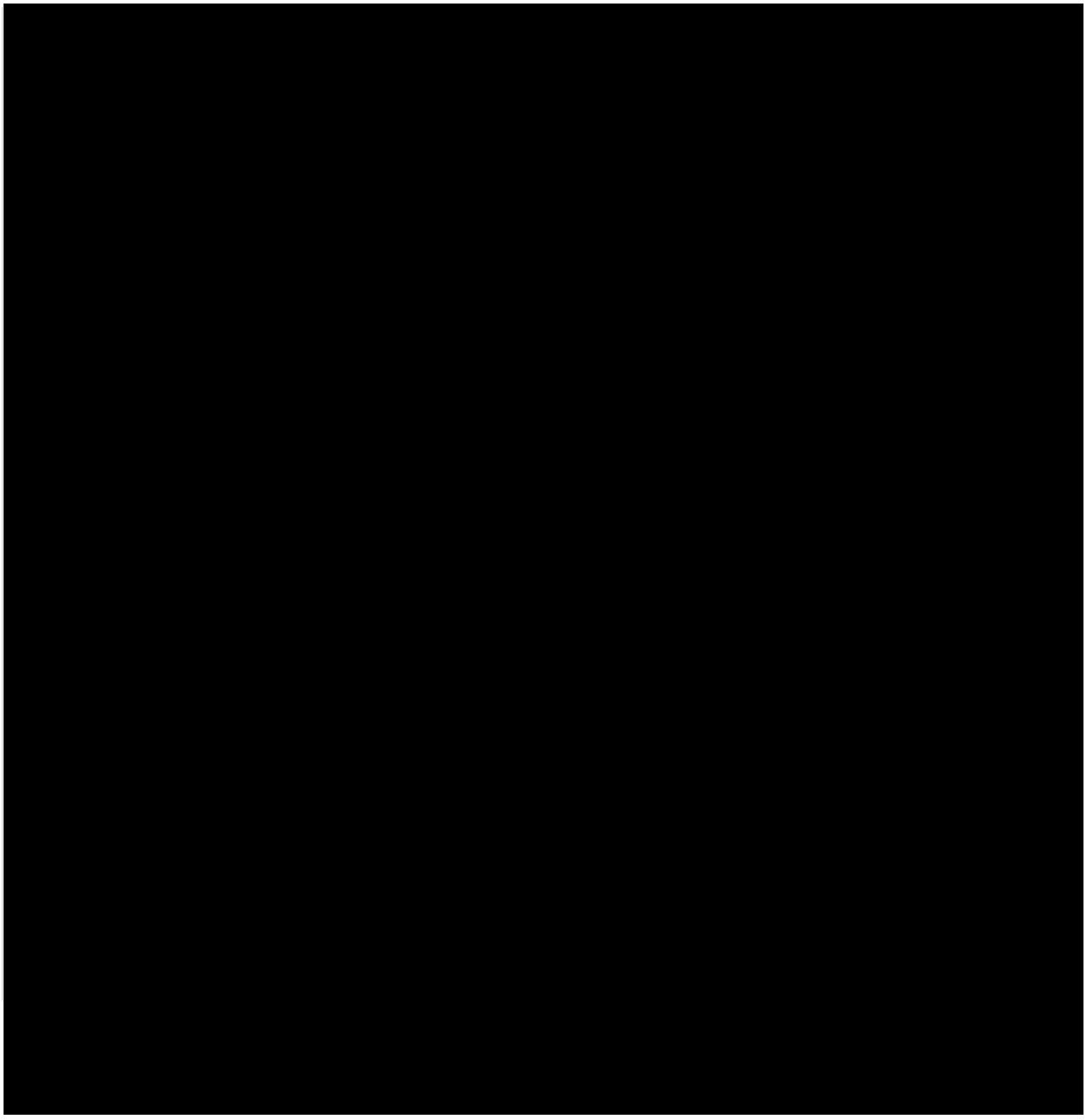
10.7.1 Cold Urticaria activity score (ColdUAS)



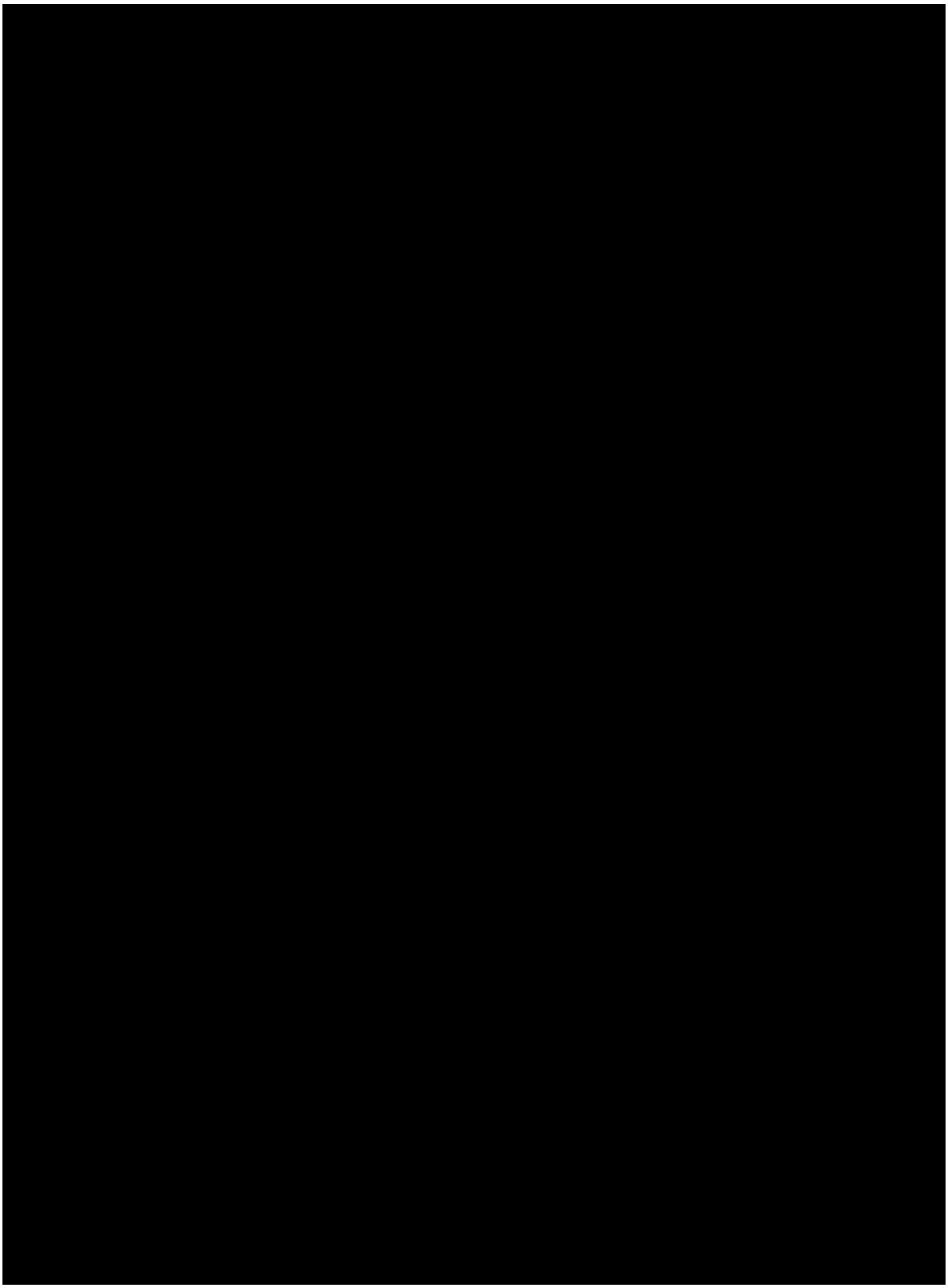




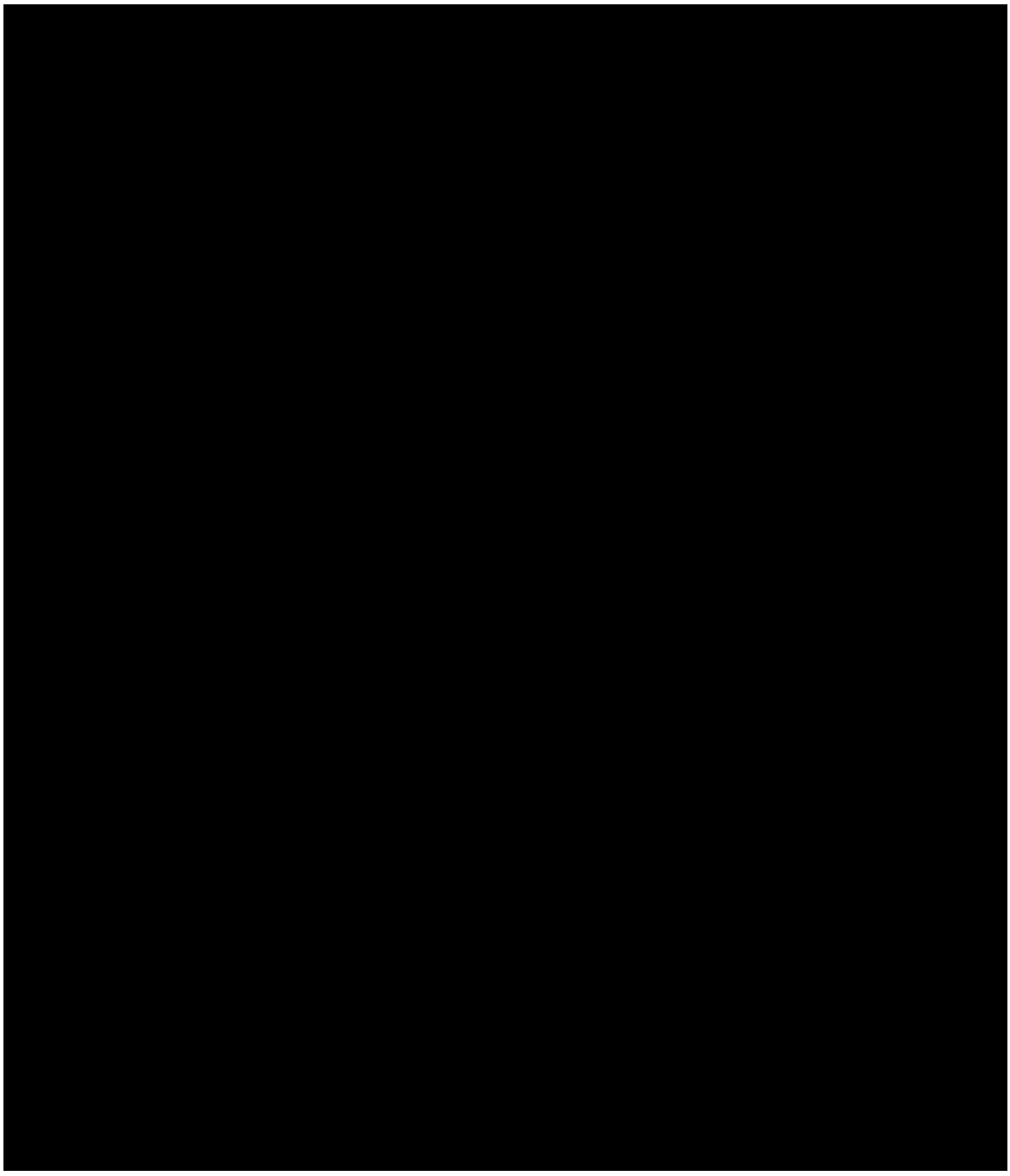
10.7.2 Acquired Cold Urticaria Severity Index



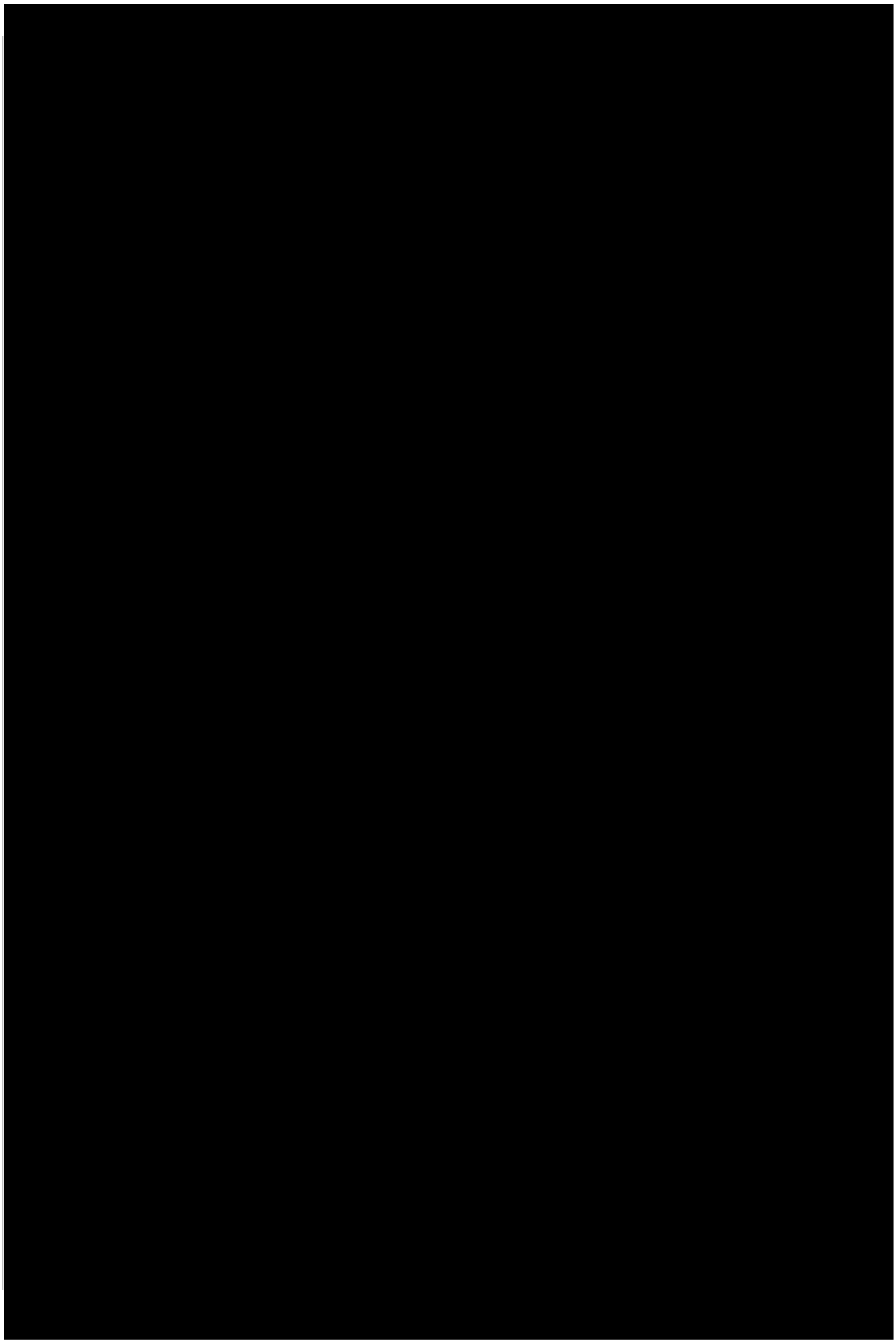
10.7.3 Itch numerical rating scale, pain numerical rating scale, and burning sensational numerical rating scale

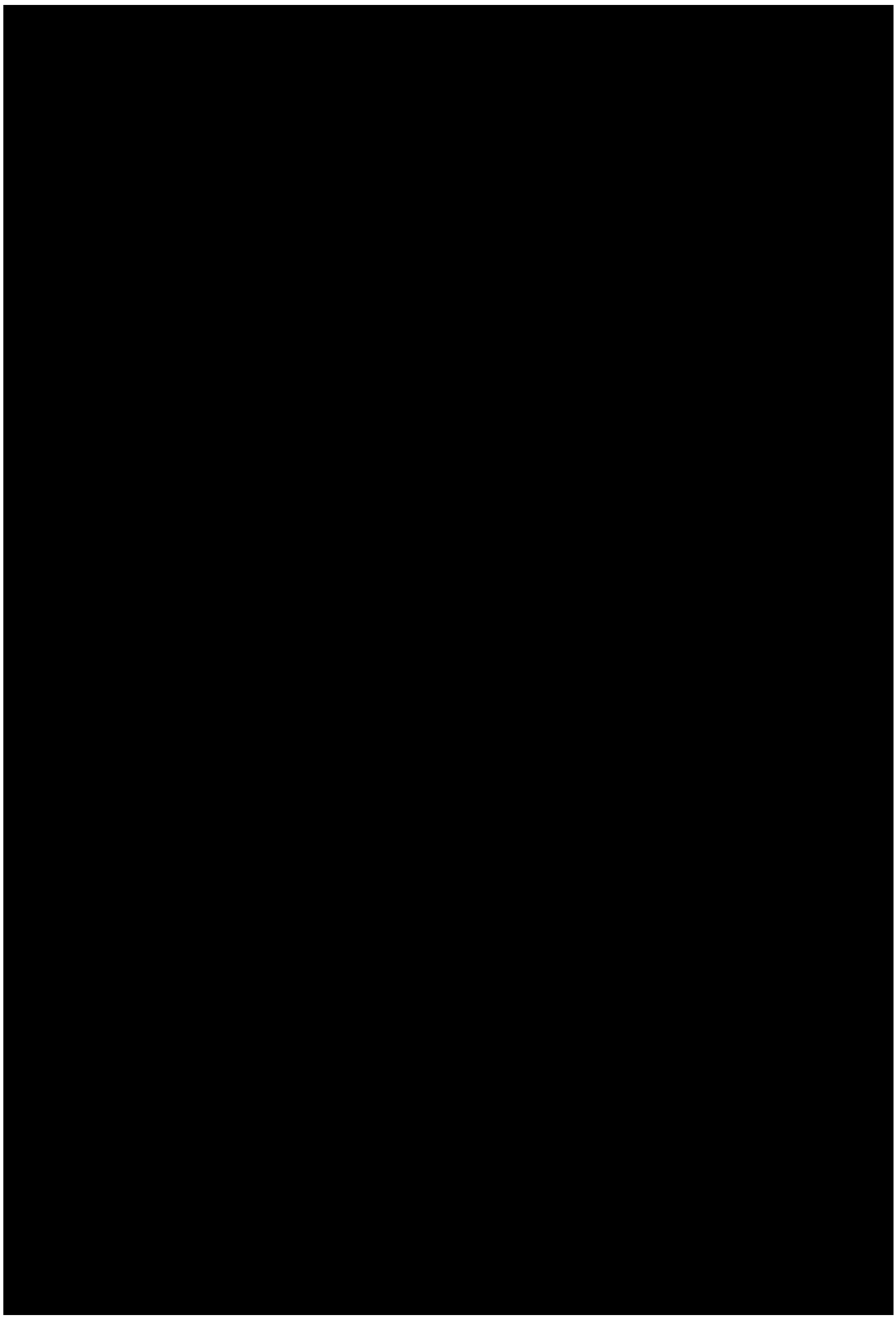


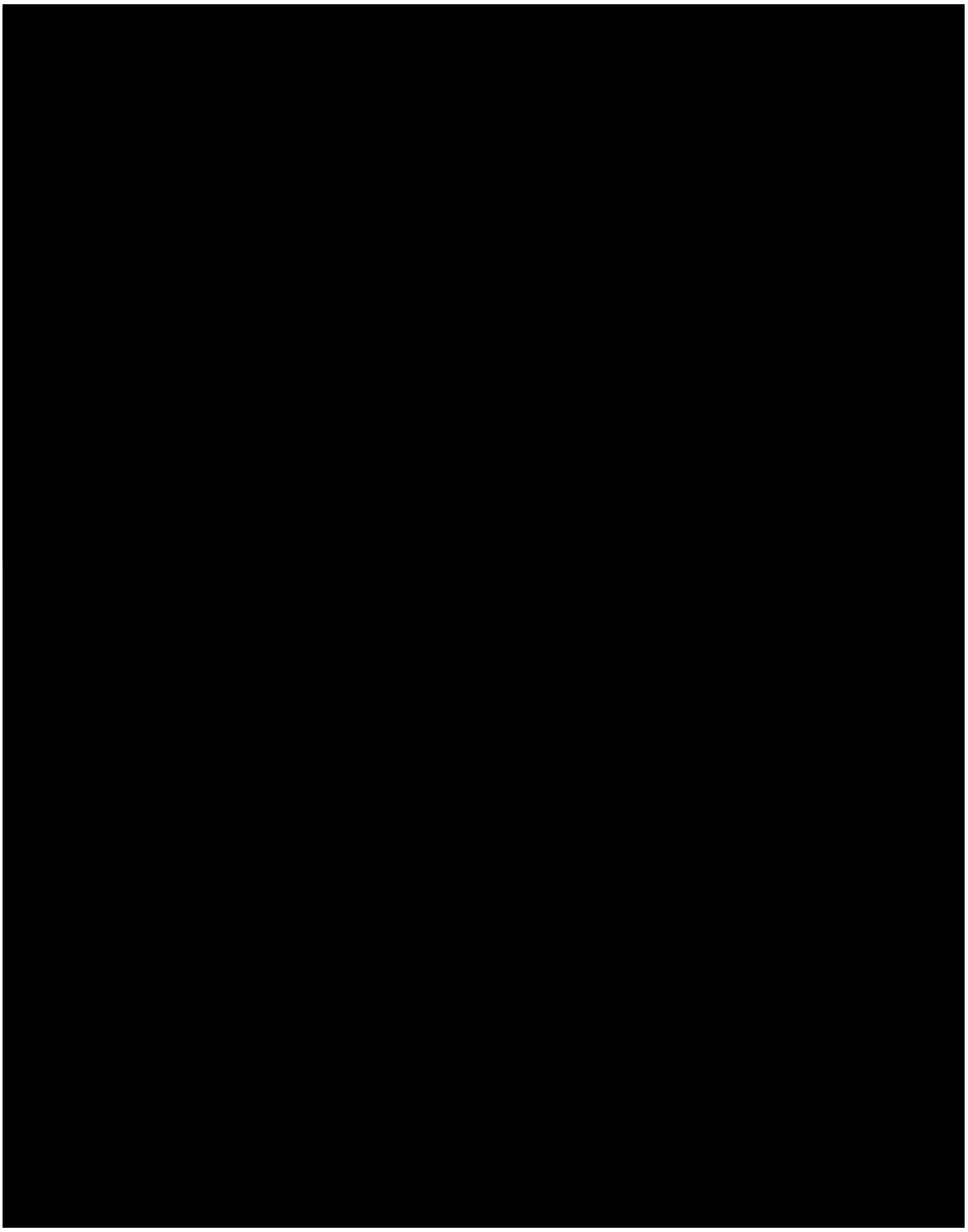
10.7.4 Wheal Intensity Likert Scale



10.7.5 ColdU-QoL

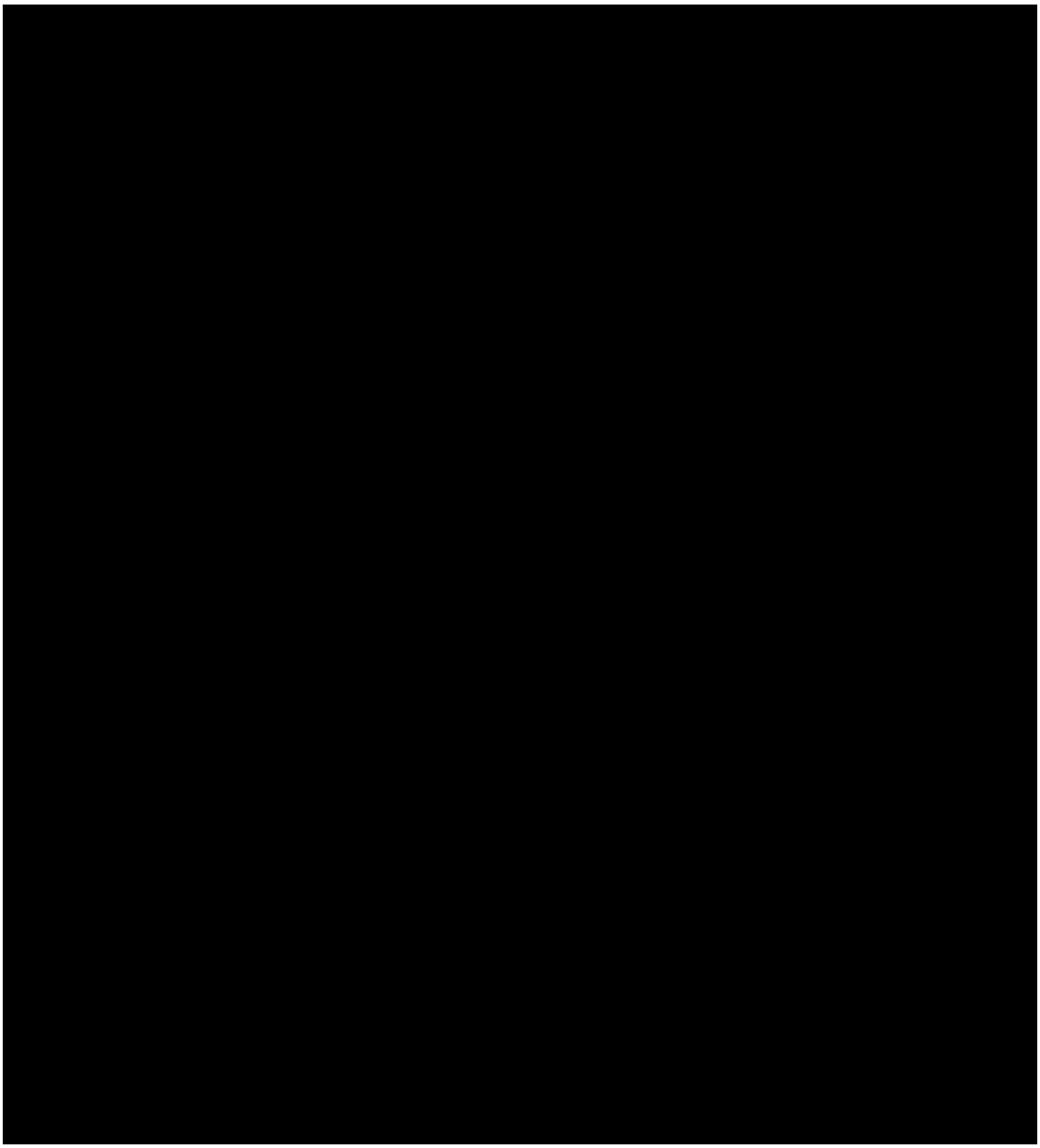




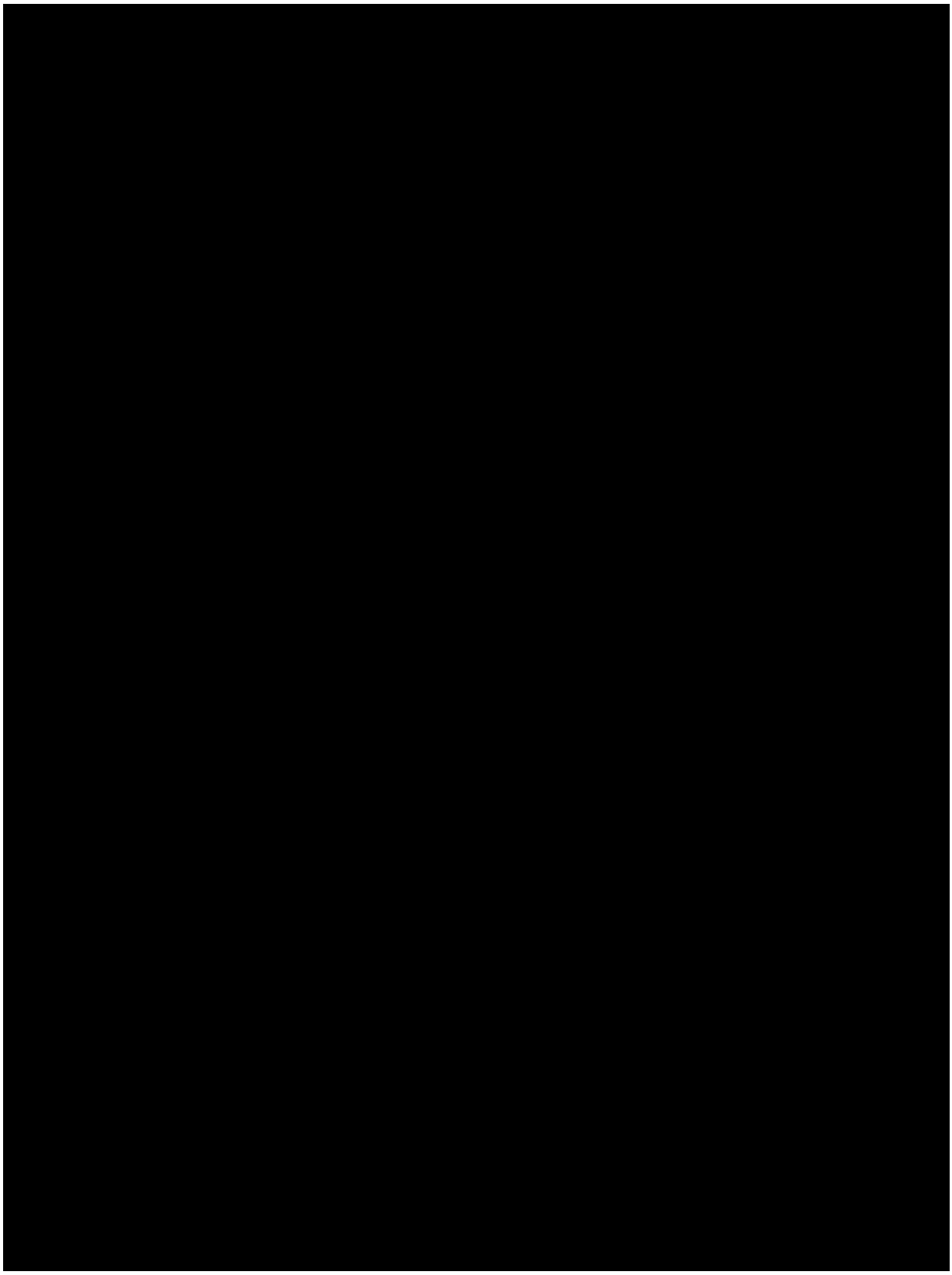


10.7.6 Urticaria control test (UCT)

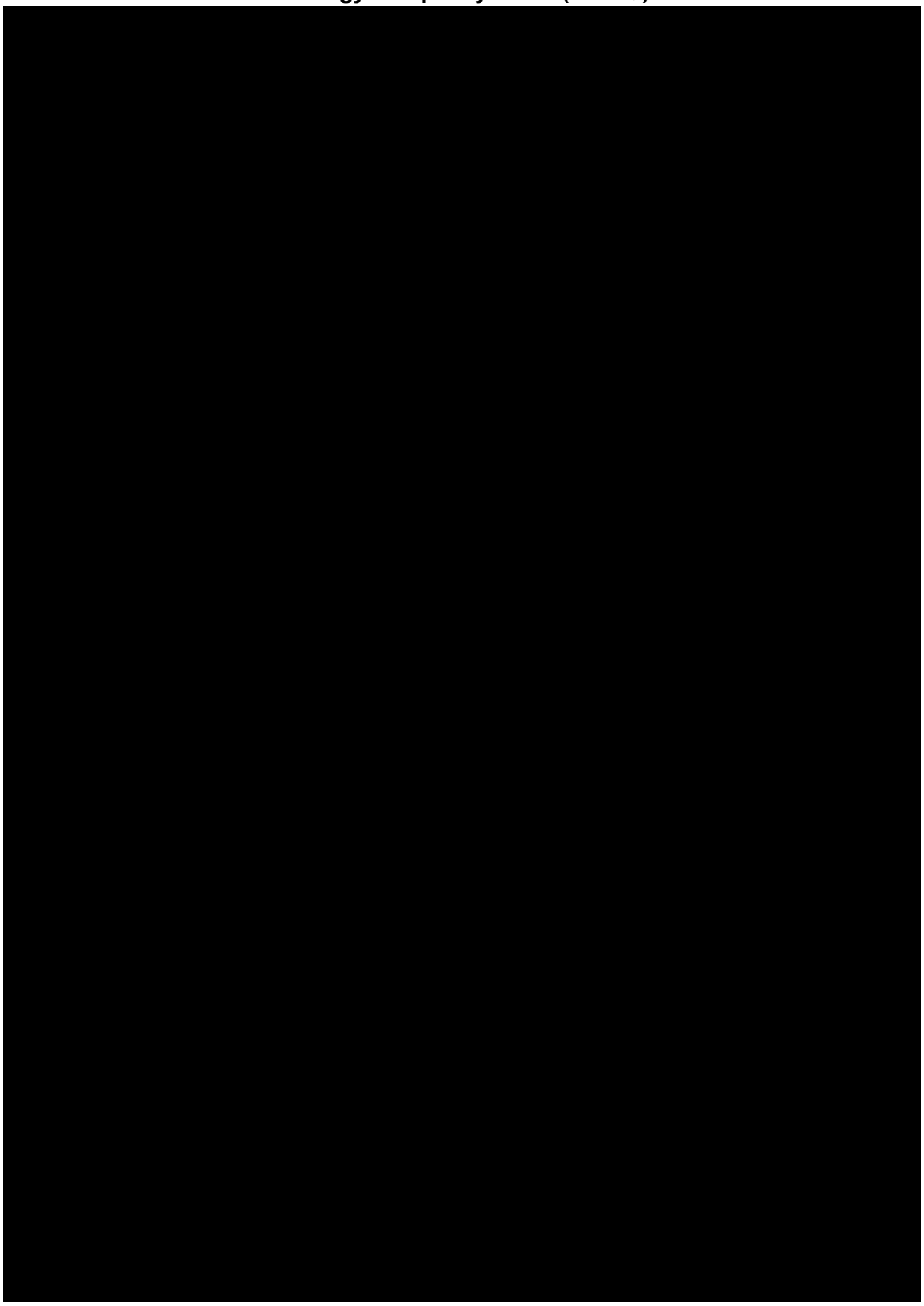
[1]



10.7.7 Dermatology life quality index (DLQI)



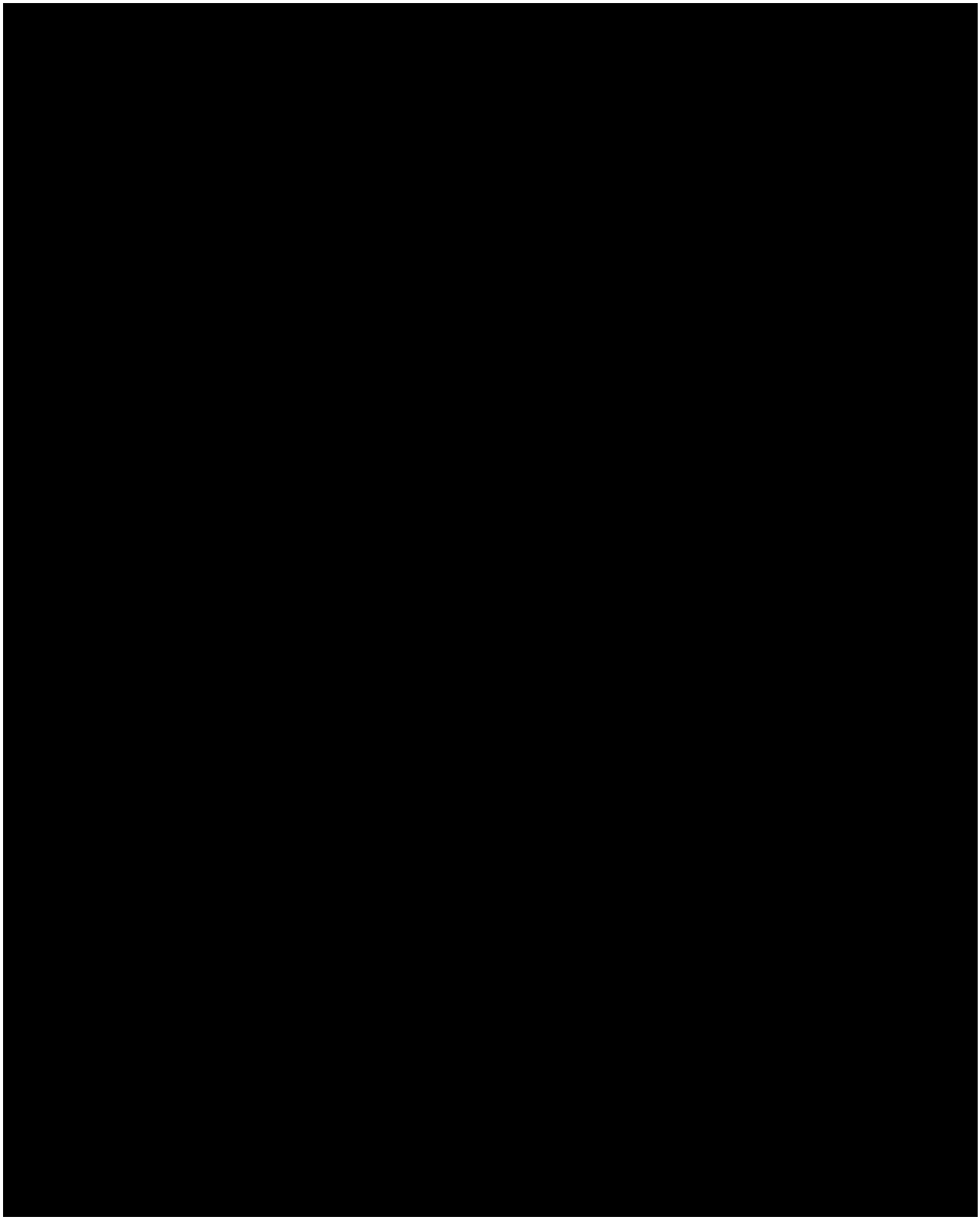
10.7.8 Children's dermatology life quality index (CDLQI)

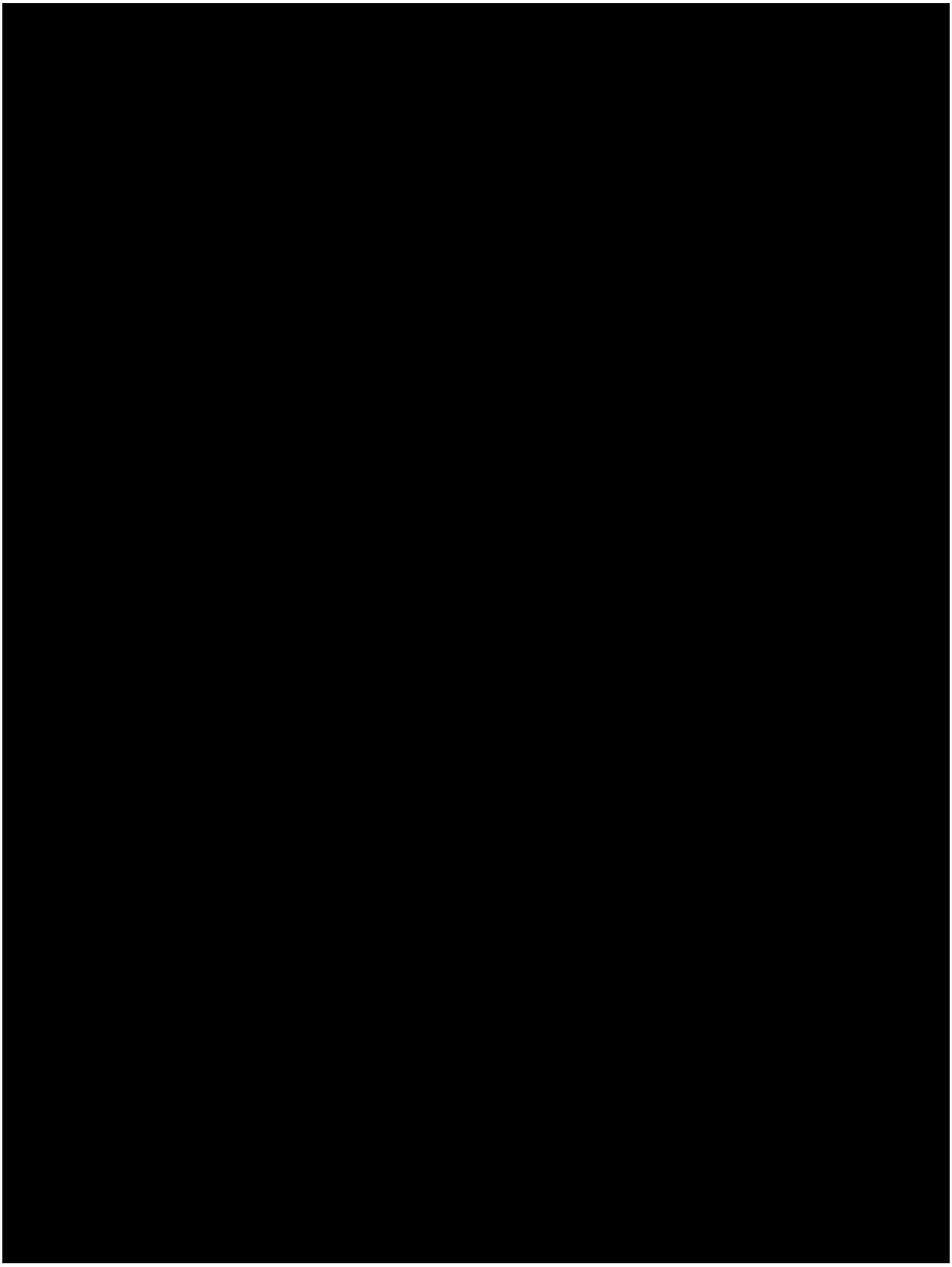


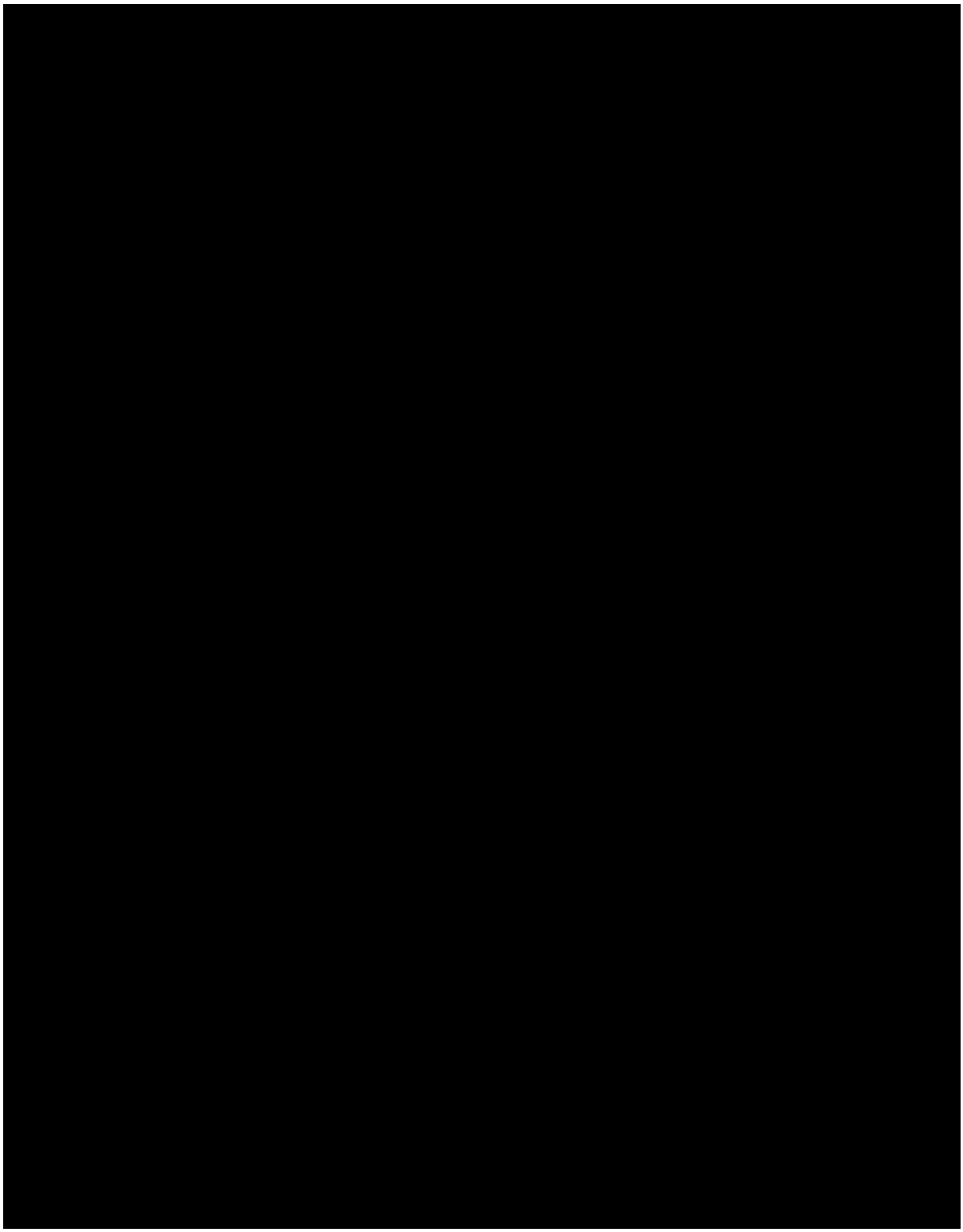
10.7.9 Patient Global Impression of Change

10.7.10 Patient Global Impression of Severity

10.7.11 5-level EuroQol 5-dimensional questionnaire (EQ-5D-5L)







10.8 APPENDIX 8: COUNTRY SPECIFIC REQUIREMENTS

10.8.1 Japan

Section 6.5.1 **Rescue medicine** (see Section 6.5.1)

Use of H1-antihistamines for chronic inducible cold urticarial treatment

In Japan, patients with chronic inducible ColdU who are not well-controlled on approved H1-antihistamine dose may escalate the H1-antihistamine dose only up to 2-fold the approved dose.

During the study, participants should continue their established standard of care background therapy with a long-acting non-sedating H1-antihistamine, at up to 2-fold the approved dose for CSU.

- Participants who used H1-antihistamine regularly/daily prior to study entry should continue to take it daily. Note: regular/daily use of H1-antihistamine prior to study entry is defined as H1-antihistamine intake for at least 4 days per week for at least 1 month prior to screening visit (Visit 1)
- Participants who took H1-antihistamine as needed prior to study entry should limit the use to short-term.

Rescue therapy

All participants will be allowed to take additional doses of their H1-antihistamine medications as rescue therapy as long as they do not exceed 2-fold the approved dose during the screening, treatment, and follow-up periods. If symptoms are still uncontrolled after increase of H1-antihistamine to the maximum allowed dose, or if the participant is already on the 2-fold approved H1-antihistamine, the participants can switch to another antihistamine up to 2-fold approved dose for CSU or a short course of OCS is allowed as rescue therapy during the treatment and follow-up periods.

Due to an episodic nature of ColdU, it is recommended to prescribe rescue therapy for a short period of time (not more than 7 days).In order to ensure consistency, when possible, it is recommended to use a short course of OCS for 5 to 7 days with a starting dose of oral prednisone 40 mg (or clinically comparable OCS) followed by taper per the Investigator's judgment.

The ice cube provocation test should be delayed if rescue therapy (H1-antihistamine or OCS) is taken within 5 days prior to the test. The ice cube provocation test can be done when the participant is back to prescreening H1-antihistamine dose or is off H1-antihistamine (or OCS) intake for at least 5 consecutive days to allow to have ice cube provocation test performed under the same background condition for each participant from screening visit (Visit 1) to EOS (Visit 5).

The initial background therapy should remain unchanged throughout the study. Participants should continue their prescreening dose of initial H1-antihistamine once rescue treatment is no longer required or stop H1-antihistamine intake.

The use of permitted rescue medications should be delayed, if possible, for at least 8 weeks following the initiation of the investigational treatment. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

For other information related to H1-antihistamine and OCS including safety precautions please refer to the locally approved product labeling.

10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

Continuation of the study in the event of a regional or national emergency declared by a governmental agency:

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, terrorist attack) may prevent access to the clinical trial site.

Contingency procedures are suggested for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with GCP in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.

Study Intervention Administration

The following contingencies may be implemented for the duration of the emergency (after Sponsor agreement is obtained) to make clinical supplies available to the participant for the duration of the emergency:

- In case of emergency (eg, natural disaster, pandemic, etc.), IMP may be supplied from the site to the participant via a Sponsor-approved courier company where allowed by local regulations and approved by the participant (or parent/legally authorized representative).
- When the participant has a study visit, the IMP will be administered following clinical procedures and blood collection. Participants should be monitored for at least 30 minutes. The monitoring period may be extended as per country specific or local study center-specific requirements.

Temporary discontinuation/rechallenge

In addition, for a regional or national emergency declared by a governmental agency, the temporary discontinuation will be allowed as defined in Section 7.1.2.

During a regional or national emergency declared by a governmental agency, reinitiation of IMP can only occur once the Investigator has determined, according to his/her best judgment, that the contribution of the IMP(s) to the occurrence of the epidemic event (eg. COVID-19) was unlikely.

Study Assessments and Procedures

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study. During the emergency, if the site will be unable to adequately follow protocol mandated procedures, alternative treatment outside the clinical trial should be proposed, and

screening/enrollment/randomization/administration of study intervention may be temporarily delayed (see also Section 5.5).

In the event of a regional or national emergency declared by a governmental agency, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms, such as phone contact, virtual visits, online meetings, extension of visit windows for on-site visits, use of local clinic or laboratory locations, and home visits by skilled staff. The primary focus should be collection of safety information and provision of daily e-diary data collection for key efficacy assessments. Implementation of such mechanisms may differ country by country, depending on country regulations and local business continuity plans. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 (or any other pandemic) will be granted. All temporary mechanisms utilized, and deviations from planned study procedures are to be documented as being related to COVID-19 (or any other public health emergency) and will remain in effect only for the duration of the public health emergency. Contingencies implemented due to emergency will be documented.

Statistical Consideration

The impact of the regional or national emergency declared by a governmental agency on study conduct will be summarized (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency). Data collected regarding the impact of the COVID-19 or other pandemics on the participants will be summarized (eg, discontinuation due to COVID-19). Any additional analyses and methods required to investigate the impact of COVID-19 or other events requiring public health emergency on the efficacy (eg, missing data due to COVID-19) and safety will be detailed in the SAP.

Informed Consent Process

For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participant or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension, use of local laboratories).

10.10 APPENDIX 10: DEFINITION OF ANAPHYLAXIS

"Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death (39)".

Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; *BP*, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

10.11 APPENDIX 11: LIST OF OPPORTUNISTIC INFECTIONS

- Aspergillosis
- Blastomyces dermatitidis (endemic in the south-eastern and south-central states US, along Mississippi and Ohio Rivers)
- Candidiasis - only systemic or extensive mucosal or cutaneous candidiasis
- Coccidioides immitis (endemic south-western US and Central and South America)
- Cryptococcus
- Cytomegalovirus
- Herpes Simplex (disseminated)
- Herpes Zoster (disseminated; ophthalmic; involvement of 2 or more dermatomes)
- Histoplasmosis (pulmonary or disseminated; most common tropical areas Tennessee-Ohio-Mississippi river basins)
- Listeriosis
- Mycobacterium TB
- Mycobacterium avium
- Non-TB mycobacteria
- Pneumocystis pneumonia

This list is indicative and not exhaustive.

10.12 APPENDIX 12: LIST OF PROHIBITED LIVE ATTENUATED VACCINES

- Bacillus Calmette-Guérin (BCG) anti-TB vaccine
- Chickenpox (Varicella)
- Intranasal influenza (FluMist-Influenza); inactive influenza vaccine delivered by injection is permitted
- Measles (Rubeola)
- Measles-mumps-rubella combination
- Measles-mumps-rubella-varicella combination
- Mumps
- Oral polio (Sabin)
- Oral typhoid
- Rotavirus
- Rubella
- Smallpox (Vaccinia)
- Varicella Zoster (shingles)
- Yellow fever

This list is indicative and not exhaustive.

10.13 APPENDIX 13: ESTIMANDS FOR MAIN ENDPOINTS

Table 11 - Summary of primary estimand for main endpoints in ColdU study

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) strategy and missing data handling**	**Population-level summary**
Primary objective: To demonstrate the efficacy of dupilumab in adult and adolescent participants with primary acquired chronic inducible ColdU who remain symptomatic despite the use of an H1-antihistamine				
Primary endpoint (treatment policy/composite estimand)	Proportion of participants with negative ice cube provocation test at Week 24	ITT	Discontinuation of the study intervention before Week 24 (but not taking highly influential prohibited medications and/or highly influential rescue medications prior to Week 24): Off-study intervention data up to Week 24 will be included in the analysis (treatment policy strategy). Taking highly influential prohibited medications and/or highly influential rescue medications prior to Week 24: Participants will be considered as having positive ice cube provocation tests at Week 24 (composite strategy). Having missing data at Week 24: Participants will be considered as having positive ice cube provocation tests at Week 24.	CMH test stratified by region (combined countries) and background H1-antihistamine regular/daily use (Yes/No). The comparison of the proportions of treatment response between dupilumab and placebo will be derived, and the corresponding odd ratios and the 95% CI will be reported.
Secondary objective: To demonstrate the efficacy of dupilumab on primary acquired chronic inducible ColdU local signs and symptoms				
Secondary endpoint (treatment policy/composite estimand)	Change from baseline in local wheal intensity at the provocation site at Week 24 using the wheal intensity Likert scale ranging from 0 to 5 (clinician evaluation)	ITT	The intercurrent events will be handled as below: • Discontinuation of the study intervention before Week 24 (but not taking highly influential prohibited medications and/or highly influential rescue medications prior to Week 24): Off-study intervention data up to Week 24 will be included in the analysis (treatment policy strategy)	ANCOVA model with treatment group, baseline value, region, and background H1-antihistamine regular/daily use (Yes/No) as covariates will be used. Statistical inference obtained from all imputed data by ANCOVA model will be combined using Rubin's rule.

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) strategy and missing data handling**	**Population-level summary**
	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	ITT	• Taking highly influential prohibited medications and/or highly influential rescue medications prior to Week 24: data will be set to missing values after the medication usage, and the WOCF approach (worst postbaseline observation for the participant will be carried forward) will be used to impute missing endpoint value (for participants whose postbaseline values are all missing, the participant's baseline value will be used to impute the missing endpoint value) (composite strategy) Missing data handling: • For participants who discontinue study intervention due to lack of efficacy, all data collected after discontinuation will be used in the analysis, and a WOCF approach will be used to impute missing Week 24 value if needed. For participants who discontinue study intervention not due to lack of efficacy, a multiple imputation approach will be used to impute missing Week 24 value, and this multiple imputation will use all participants excluding participants who have taken the highly influential prohibited medications and/or highly influential rescue medications on or before Week 24 and excluding patients who discontinue due to lack of efficacy on or before Week 24.	Descriptive statistics including number of participants, mean, standard error, and least squares (LS) mean changes (and standard error) score will be provided. In addition, difference of the dupilumab group against placebo in LS means and the corresponding 95% CI will be provided along with the p-values.

Abbreviations: ANCOVA = Analysis of covariance, CI = confidence interval, CMH = Cochran-Mantel-Haenszel, ColdU = cold urticaria, ITT= Intent-to-treat.
Additional secondary objectives/endpoints are not included in this table but would be handled with a similar strategy as the endpoint type (ie, continuous, proportion) at other weeks.

10.14 APPENDIX 14: ABBREVIATIONS

ACU:	acquired cold urticaria
ACUSI:	Acquired Cold Urticaria Severity Index
AD:	atopic dermatitis
ADA:	antidrug antibody
ADR:	adverse drug reaction
AEs:	adverse event(s)
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
ANCOVA:	Analysis of covariance
CDLQI:	Children's Dermatology Life Quality Index
CFR:	Code of Federal Regulations
CholU:	cholinergic urticaria
CI:	confidence interval
CIndU:	Chronic Inducible Urticaria
ColdU:	cold urticaria
ColdUAS:	Cold Urticaria Activity Score
ColdU-QoL:	Cold Urticaria Quality of Life
COPD:	chronic obstructive pulmonary disease
COVID-19:	Coronavirus Disease 2019
CRF:	case report form
CRSwNP:	chronic rhinosinusitis with nasal polyposis
CSICF:	Core Study Informed Consent Form
CSR:	clinical study report
CSTT:	cold-simulation time test
CSU:	Chronic Spontaneous Urticaria
DLQI:	Dermatology Life Quality Index
DNA:	Deoxyribonucleic acid
DPU:	delayed pressure urticaria
DTP:	direct to patient
ECG:	electrocardiogram
eCRF:	electronic case report form
ELISA:	enzyme-linked immunosorbent assay
EoE:	eosinophilic esophagitis
EOT:	end of treatment
EQ-5D:	EuroQol-5 dimensions
EQ-5D-5L:	5-level EuroQol 5 dimensional questionnaire
EQ-VAS:	EuroQol visual analogue scale
EU:	European Union
FcεRI:	Fc epsilon receptor
GCP:	Good Clinical Practice
GDPR:	General Data Protection Regulation
HBc Ab:	hepatitis B core antibody

HBs Ag:	hepatitis B virus surface antigen
HBV:	hepatitis B virus
HCV:	hepatitis C virus
HCV Ab:	Hepatitis C antibody
HIV:	human immunodeficiency virus
HRQoL:	health-related quality of life
HRT:	hormone replacement therapy
IB:	Investigator's brochure
ICF:	informed consent form
ICH:	International Council of Harmonisation
IEC:	Institutional Ethics Committee
IgE:	immunoglobulin E
IL:	Interleukin
IL-4Rα:	interleukin-4 receptor alpha subunit
IMP:	investigational medicinal product
IRB:	Institutional Review Boards
IRT:	interactive response technology
ITT:	Intent-to-treat
IVIG:	intravenous immunoglobulin
IVRS:	interactive voice response system
IWRS:	interactive web response system
LS:	least squares
LTE4:	leukotriene E4
LTRAs:	Leukotriene receptor antagonists
mAb:	monoclonal antibody
MID:	minimal important difference
NIMP:	noninvestigational medicinal product
NRS:	Numerical Rating Scale
OCS:	oral corticosteroids
PD:	pharmacodynamics
PGDM:	prostaglandin D2 metabolite
PGIC:	Patient Global Impression of Change
PGIS:	Patient Global Impression of Severity
PK:	pharmacokinetics
PN:	prurigo nodularis
PRO:	patient-reported outcome
q2w:	every 2 weeks
qd:	once per day
QoL:	Quality of Life
RNA:	ribonucleic acid
SAE:	serious adverse event
SAP:	statistical analysis plan
SC:	subcutaneous
SCS:	systemic corticosteroids
SoA:	schedule of activities
SUSAR:	suspected unexpected serious adverse reactions

TB:	tuberculosis
TEAE:	treatment-emergent adverse event
Th2:	T helper 2
UCT:	urticaria control test
ULN:	upper limit of normal
US:	United States
WOCBP:	woman of childbearing potential
WOCF:	worst observation carried forward

10.15 APPENDIX 15: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC).

11 REFERENCES

1. Magerl M, Altrichter S, Borzova E, Giménez-Arnau A, Grattan CE, Lawlor F, et al. The definition, diagnostic testing, and management of chronic inducible urticarias - The EAACI/GA(2) LEN/EDF/UNEV consensus recommendations 2016 update and revision. Allergy. 2016;71(6):780-802.

2. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, et al. The EAACI/GA(2)LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy. 2018;73(7):1393-414.

3. Maurer M, Hawro T, Krause K, Magerl M, Metz M, Siebenhaar F, et al. Diagnosis and treatment of chronic Inducible Urticaria. Allergy. 2019;74(12):2250-3.

4. Maurer M, Fluhr JW, Khan DA. How to Approach Chronic Inducible Urticaria. J Allergy Clin Immunol Pract. 2018;6(4):1119-30.

5. Stepaniuk P, Vostretsova K, Kanani A. Review of cold induced urticaria characteristics, diagnosis and management in a Western Canadian allergy practice. Allergy Asthama Clin Immunol 2018;14:85.

6. Neittaanmaki H. Cold urticaria: clinical findings in 220 patients. J Am Acad Dermatol. 1985;13(4):636-44.

7. Dressler C, Werner RN, Eisert L, Zuberbier T, Nast A, Maurer M. Chronic inducible urticaria: A systematic review of treatment options. J Allergy Clin Immunol. 2018;141(5):1726-34.

8. Maurer M, Metz M, Brehler R, Hillen U, Jakob T, Mahler V, et al. Omalizumab treatment in patients with chronic inducible urticaria: A systematic review of published evidence. J Allergy Clin Immunol. 2018;141(2):638-9.

9. Metz M, Schütz A, Weller K, Gorczyza M, Zimmer S, Staubach P, et al. Omalizumab is effective in cold urticaria-results of a randomized placebo-controlled trial. J Allergy Clin Immunol. 2017;140(3):864-7.

10. Guillén-Aguinaga S, Jáuregui Presa I, Aguinaga-Ontoso E, Guillén-Grima F, Ferrer M. Updosing Nonsedating Antihistamines in Patients With Chronic Spontaneous Urticaria: A Systematic Review and Meta-Analysis. Br J Dermatol. 2016;175(6):1153-65.

11. Dellon ES, Peterson KA, Murray JA, Falk GW, Gonsalves N, Chehade M, et al. AK002 (Antolimab) in adult patients with active eosinophilic gastritis and/or eosinophilic gastroenteritis: Primary results from a randomized, double-blind, placebo controlled phase 2 trial (ENIGMA Study). American College of Gastroenterology - ACG 2019. San Antonio, Texas. 25-30 October 2019.

12. Lee JK, Simpson RS. Dupilumab as a novel therapy for difficult to treat chronic spontaneous urticaria. J Allergy Clin Immunol Pract. 2019;7(5):1659-61.

13. Ferrucci S, Benzecry V, Berti E, Asero R. Rapid disappearance of both severe atopic dermatitis and cold urticaria following dupilumab treatment. Clinl Exp Dermatol. 2020;45(3):345-6.

14. Möller A, Henning M, Zuberbier T, Czarnetzki-Henz BM. Epidemiology and clinical aspects of cold urticaria. Hautarzt. 1996;47:510–514.

15. Kaplan AP. Chronic spontaneous urticaria: pathogenesis and treatment considerations. Allergy Asthma Immunol Res. 2017;9(6):477-82.

16. Maurer M, Rosén K, Hsieh HJ, Saini S, Grattan C, Gimenéz-Arnau A, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med. 2013;368(10):924-35.

17. Church MK, Kolkhir P, Metz M, Maurer M. The role and relevance of mast cells in urticaria. Immunol Rev. 2018;282(1):232-47.

18. Le Floc'h A, Allinne J, Nagashima K, Scott G, Birchard D, Asrat S, et al. Distinct and overlapping roles of IL-4 and IL-13 in driving type 2 inflammation. Poster session presented at: Origins of Allergic Disease: Microbial, Epithelial and Immune Interactions. Keystone Symposia on Molecular and Cellular Biology.Tahoe City, CA.2019 Mar:25-27.

19. Fish SC, Donaldson DD, Goldman SJ, Williams CM, Kasaian MT. IgE generation and mast cell effector function in mice deficient in IL-4 and IL-13. J Immunol. 2005;174(12):7716-24.

20. Jonstam K, Swanson BN, Mannent LP, Cardell LO, Tian N, Wang Y. Dupilumab reduces local type 2 pro-inflammatory biomarkers in chronic rhinosinusitis with nasal polyposis. Allergy. 2019;74:743-52. Available from: URL:https://doi.org/10.1111/all.13685

21. Beck LA, Thaçi D, Hamilton JD, Graham NM, Bieber T, Rocklin R, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med. 2014;371:130-9.

22. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med. 2018;378:2486-96.

23. Magerl M, Pisarevskaja D, Staubach P, Martus P, Church MK, Maurer M. Critical temperature threshold measurement for cold urticaria: a randomized controlled trial of H(1) -antihistamine dose escalation. Br J Dermatol. 2012;166(5):1095-9.

24. Kulthanan K, Hunnangkul S, Tuchinda P, Chularojanamontri L, Weerasubpong P, Subchookul C, et al. Treatments of cold urticaria: A systematic review. J Allergy Clin Immunol. 2019;143:1311-31.

25. Weller K, Groffik A, Church MK, Hawro T, Krause K, Metz M, et al. Development and validation of the Urticaria Control Test: a patient-reported outcome instrument for assessing urticaria control. J Allergy Clin Immunol. 2014;133(5):1365-72.

26. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. Clin Exp Dermatol.1994;19(3):210-6.

27. European Commission website. Ethical considerations for clinical trials on medicinal products conducted with minors. Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use; 2017: 1-48. [Cited on: 2020 August 20] Available from: URL:https://ec.europa.eu/health/sites/health/files/files/eudralex/vol10/2017_09_18_ethical_consid_ct_with_minors.pdf

28. Metz M, Scholz E, Ferrán M, Izquierdo I, Giménez-Arnau A, Maurer M. Rupatadine and Its Effects on Symptom Control, Stimulation Time, and Temperature Thresholds in Patients With Acquired Cold Urticaria. Ann Allergy Asthma Immunol. 2010;104(1):86-92.

29. Dubertret L, Pecquet C, Murrieta-Aguttes M, Leynadier F. Mizolastine in primary acquired cold urticaria. J Am Acad Dermatol. 2003;48(4):578-83.

30. Yosipovitch G, Reaney M, Mastey V, Eckert L, Abbé A, Nelson L, et al. Peak Pruritus Numerical Rating Scale: psychometric validation and responder definition for assessing itch in moderate-to-severe atopic dermatitis. Br J Dermatol. 2019;181(4):761-9.

31. Ohanyan T, Schoepke N, Bolukbasi B, Metz M, Hawro T, Zuberbier T, et al. Responsiveness and minimal important difference of the urticaria control test. J Allergy Clin Immunol. 2017;140(6):1710-3.

32. Chernyshov PV. The evolution of quality of life assessment and use in dermatology. Dermatology. 2019;235(3):167-74.

33. Shikiar R, Harding G, Leahy M, Lennox RD. Minimal important difference (MID) of the Dermatology Life Quality Index (DLQI): results from patients with chronic idiopathic urticaria. Health Qual Life Outcomes. 2005;3:36.

34. Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. Br J Dermatol.1995;132(6):942-9.

35. Siebenhaar F, Degener F, Zuberbier T, Martus P, Maurer M. High-dose Desloratadine Decreases Wheal Volume and Improves Cold Provocation Thresholds Compared With Standard-Dose Treatment in Patients With Acquired Cold Urticaria: A Randomized, Placebo-Controlled, Crossover Study.J Allergy Clin Immunol. 2009;123(3):672-9.

36. EuroQol Group. EuroQol-A new facility for the measurement of helth-related quality of life. Health Policy. 1990;16(3):199-208.

37. Simons FER, Ardusso LRF, Bilò MB, Cardona V, Ebisawa M, El-Gamal YM. International consensus on (ICON) anaphylaxis. World Allergy Organization Journal. 2014;7(1):9.

38. Wanderer AA, Grandel KE, Wasserman SI, Farr RS. Clinical characteristics of cold-induced systemic reactions in acquired cold urticaria syndromes: recommendations for prevention of

this complication and a proposal for a diagnostic classification of cold urticaria. J Allergy Clin Immunol. 1986;78:417-23.

39. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report - Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117:391-7.

Signature Page for VV-CLIN-0635063 v1.0
efc16720-16-1-1-amended-protocol01

Approve & eSign	[redacted]

Approve & eSign	[redacted]