AMENDED CLINICAL TRIAL PROTOCOL 05

Protocol title:	**Master protocol of three randomized, double-blind, placebo-controlled, multi-center, parallel-group studies of dupilumab in patients with chronic spontaneous urticaria (CSU) who remain symptomatic despite the use of H1 antihistamine treatment in patients naïve to omalizumab and in patients who are intolerant or incomplete responders to omalizumab**
Protocol number:	**EFC16461**
Amendment number:	**05**
Compound number (INN/Trademark):	**SAR231893/REGN668 dupilumab/Dupixent**
Study phase:	**Phase 3**
Short title:	**Dupilumab for the treatment of chronic spontaneous urticaria in patients who remain symptomatic despite the use of H1 antihistamine and who are naïve to, intolerant of, or incomplete responders to omalizumab** **LIBERTY-CSU CUPID (Chronic Urticarial Pruritus Itch Dupilumab Trial)**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 05	All	17 March 2022, version 1 (electronic 5.0)
Amended Clinical Trial Protocol 04	All	29 April 2021, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 03	France only	09 October 2020, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 02	All	30 April 2020, version 1 (electronic 2.0)
Amended Clinical Trial Protocol 01	Japan only	10 February 2020, version 1 (electronic 1.0)
Original Protocol		24 October 2019, version 1 (electronic 4.0)

Amended protocol 05 (17 March 2022)

This amended protocol 05 (Amendment 05) 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

EFC16461 is a double-blind placebo-controlled phase 3 study in patients with chronic spontaneous urticaria (CSU) who remain symptomatic despite the use of H1 antihistamine (H1-AH) treatment, composed of Study A conducted in patients naïve to omalizumab and Study B in patients who are intolerant or incomplete responders to omalizumab.

The primary purpose of this amendment is to conduct a Study C with a study population and design similar to the completed Study A, to meet Health Authority requirements to provide data from two adequate and well-controlled clinical trials to support filing of a marketing application.

In addition, key Study A results and information on the Study B prespecified interim analysis outcome have been added to this amended protocol.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page; 1.1 Synopsis; 1.2 Schema; 1.3 Schedule of Activities (SoA); 2.1 Study rationale; 2.2 Background; 2.3 Benefit/risk assessment; 3 Objectives and Endpoints; 4.1 Overall design; 4.2 Scientific rationale for study design; 5.1 Inclusion criteria; 5.2 Exclusion criteria; 6 Study intervention; 6.3 Measures to minimize bias: randomization and blinding; 8 Study assessments and procedures; 8.8 Biomarkers; 9.1 Statistical hypotheses; 9.2 Sample Size Determination; 9.3 Populations for Analyses; 9.4.1 Efficacy Analyses; 9.5 Interim Analyses;	Study C was added, with a design similar to Study A.	Study C will be conducted in the same study population with a similar design as Study A, to meet Health Authority requirements to provide data from two adequate and well-controlled clinical trials to support filing of a marketing application.
1.1 Synopsis; 4.1 Overall design; 4.2 Scientific rationale for study design; 6.3 Measures to minimize bias: randomization and blinding	Study C will include not more than approximately 50% of participants having their H1-AH therapy at recommended doses, and not less than approximately 30% but not more than approximately 45% of participants presenting with angioedema at baseline. For Study C, in adults, in addition to randomization stratification by country, randomization will be stratified by presence of angioedema at baseline.	To maintain consistency between the study population in studies A and C, and reflect the real-life distribution of patients with angioedema and uncontrolled by both standard dose or maximal H1-AH therapy. To ensure equal distribution of patients with angioedema at baseline in both treatment groups.
1.1 Synopsis; 2.1 Study rationale; 2.3 Benefit/risk assessment; 4.2 Scientific rationale for study design; 4.3 Justification for Dose	Study A results are presented.	Study A has been completed and results are available, demonstrating dupilumab efficacy and acceptable safety in the studied population.
1.1 Synopsis; 2.1 Study rationale; 2.3 Benefit/risk assessment	Study B prespecified interim analysis outcome is presented.	The outcome of the Study B pre-specified interim analysis met the protocol efficacy statistical criteria for futility (stop for futility outcome), with no new safety concerns identified.
2.3 Benefit/Risk Assessment	Information on dupilumab marketing authorization status has been updated.	Updated to include additional marketing authorizations.
6.3 Measures to minimize bias: randomization and blinding	Change in wording regarding participant unblinding process: the Investigator may contact the Sponsor at his/her discretion prior to unblinding.	Change in template standard wording.
Whole document	Minor editorial changes were made throughout the document	

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

Master protocol of three randomized, double-blind, placebo-controlled, multi-center, parallel-group studies of dupilumab in patients with chronic spontaneous urticaria (CSU) who remain symptomatic despite the use of H1 antihistamine treatment in patients naïve to omalizumab and in patients who are intolerant or incomplete responders to omalizumab

Short title:

Dupilumab for the treatment of chronic spontaneous urticaria in patients who remain symptomatic despite the use of H1 antihistamine and who are naïve to, intolerant of, or incomplete responders to omalizumab.

LIBERTY-CSU CUPID (Chronic Urticarial Pruritus Itch Dupilumab Trial)

Rationale:

Chronic spontaneous urticaria (CSU), also referred to as chronic idiopathic urticaria (CIU), is a common condition characterized by the spontaneous appearance of itchy wheals (hives) with or without angioedema persisting for more than 6 weeks without a specific known cause. Chronic spontaneous urticaria patients with and without angioedema experience debilitating hives and pruritus secondary to mast cell and basophil dysregulation. Degranulation of these cell types by Fc gamma receptor (FcεRI) activation, through agonistic autoantibodies or cell surface-bound immunoglobulin E (IgE) cross-linked by antigen, release histamine and other pro-inflammatory mediators leading 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-antihistamines (H1-AH) is a mainstay of therapy (1). Approximately 50% of patients achieve symptomatic control with conventional H1-AH therapy (2). Even with uptitration of antihistamines, approximately 40% to 50% of patients remain symptomatic. The mechanism by which omalizumab exerts its therapeutic effects is likely constrained to reduction in serum IgE and consequent down-regulation of IgE receptors. Targeting IgE by omalizumab has been successful in treating CSU patients but not all patients are equally responsive to this therapy (3). 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-4)/interleukin-13 (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 (4, 5). Therefore, blockade of IL-4/IL-13 by dupilumab represents a novel therapeutic approach for CSU patients. In a small case series of patients who had concurrent atopic dermatitis (AD) and CSU and were resistant to omalizumab, treatment with dupilumab improved their urticaria. This further supports the rationale to target aberrant IL-4/IL-13 signaling with dupilumab in patients with CSU. As this is a novel therapy that acts further upstream than IgE-targeted therapies, the clinical trials proposed here will test the efficacy of dupilumab in

patients who have failed anti-histamines alone or who have failed both anti-histamines and omalizumab or who were intolerant to omalizumab.

Dupilumab is a fully human monoclonal antibody (mAb) directed against the interleukin-4 receptor alpha subunit (IL-4Rα), which is a component of interleukin (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 T helper 2 (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 inhibition of mast cell and basophil degranulation, and reduction of IgE serum levels and down-regulation of the Type 2 pathway may prevent or reverse the development of atopic diseases. Dupilumab has shown efficacy in multiple diseases with underlying Type 2 inflammation such as 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, decrease in urinary leukotriene E4 (LTE4) and prostaglandin D2 metabolite (PGDM) suggest inhibition of mast cells activation and release of preformed mediators.

LIBERTY-CSU CUPID Study A was completed, demonstrating the efficacy of dupilumab and an acceptable safety profile in participants with chronic spontaneous urticaria (CSU) who remain symptomatic despite the use of H1-AH treatment (6). LIBERTY-CSU CUPID Study B evaluating dupilumab in participants with CSU who are intolerant or incomplete responders to omalizumab, has completed recruitment. As prespecified in the study protocol, the Sponsor performed an interim analysis of study B. The outcome of this pre-specified interim analysis met the protocol efficacy statistical criteria for futility, with no new safety concerns identified (7). LIBERTY-CSU CUPID Study C will be conducted in the same study population as Study A and with a similar study design, to meet Health Authority requirements to provide data from two adequate and well-controlled clinical trials to support filing of a marketing application.

Objectives and endpoints

Objectives	Endpoints
Primary	
• To demonstrate the efficacy of dupilumab in study participants with CSU who remain symptomatic despite the use of H1-AH (Study A and Study C: omalizumab naïve; Study B: omalizumab intolerant or incomplete responders)	• Change from baseline in weekly itch severity score (ISS7) at Week 24 (except EU and EU reference countries) • For EU and EU reference countries only: Change from baseline in weekly urticaria activity score (UAS7, composite patient reported itch and hive score) at Week 24
Secondary	
• To demonstrate the efficacy of dupilumab on urticaria activity composite endpoint and itch or hives, separately, at various time points	• Change from baseline in weekly urticaria activity score (UAS7) at Week 12[a] and Week 24[b] (except EU and EU reference countries) • Change from baseline in ISS7 at Week 12[a] and at Week 24[b] (in EU and EU reference countries)

Objectives	Endpoints
	• Change from baseline in weekly hives severity score (HSS7) at Week 12 and Week 24 • Time to ISS7 minimally important (MID) (ISS7 ≥5) response • Proportion of ISS7 MID (≥5 points) responders at Week 12[a] and Week 24[a] • Change from baseline in ISS7 at all time points (onset of action is assessed by the first p <0.05 that remains significant at subsequent measures until Week 24) • Proportion of patients with UAS7 ≤6 at Week 12[a] and Week 24[a] • Proportion of patients with UAS7 = 0 at Week 12[a] and Week 24[a]
• To demonstrate the efficacy of dupilumab on angioedema	• Change from baseline in angioedema activity score over 7 days (AAS7) at Week 12 and Week 24
• To demonstrate the efficacy of dupilumab on urticaria control	• Change from baseline in urticaria control test (UCT) at Week 12 and Week 24 • Proportion of well-controlled patients (UCT ≥12) at Week 12 and Week 24
• 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 patients ≥16 years old, and in Children's Dermatology Life Quality Index (CDLQI) in patients ≥6 to <16 years old at Week 12 and Week 24 • Patient Global Impression of Change (PGIC) of CSU at Week 12 and Week 24 • Change from baseline in Patient Global Impression of Severity (PGIS) of CSU at Week 12 and Week 24
• To evaluate the ability of dupilumab in reducing the proportion of patients who require treatment with oral corticosteroids (OCS)	• Time-to-event and proportion of patients receiving OCS for CSU during the planned treatment period
• 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 anti-drug antibodies (ADA) against dupilumab over time

a Key secondary endpoint for Study A and Study B
b Key secondary endpoint for Study C: UAS7 at Week 24 (except EU and EU reference countries, where ISS7 at Week 24 is key secondary endpoint)

Overall design:

The master protocol EFC16461 will be comprised of 3 studies of similar design, 2 studies in participants who are omalizumab naïve (Study A and Study C) and 1 study in participants who are intolerant or incomplete responders to omalizumab (Study B). Study A and Study C will include adults, adolescents (≥12 to <18 years) and children (≥6 to <12 years in some selected countries). Study B will include adults and adolescents. The three studies are 24-week, double-blind, randomized, placebo-controlled studies to evaluate the use of dupilumab in participants with CSU who remain symptomatic despite the use of H1-AH. The studies will assess the effect of dupilumab on the itch and hives scored separately once daily and averaged over 7 days and on the

itch and hives frequency/severity through the urticaria activity score (composite) averaged over 7 days, on angioedema activity, urticaria control, and on patients' health-related quality-of-life (HRQoL), and health status.

Disclosure statement: Each Study A, B, and C is a Treatment study with 2 Parallel arms that is blinded/masked for participants and Investigators. While these are double blind trials with regard to the treatment with either dupilumab or placebo, they are 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 and children ≥6 to <12 years of age. In addition, in children, the study is not blinded to dose regimen due to the different frequency of IMP administration (q4w versus q2w).

Number of participants:

The total anticipated number of participants across the 3 studies is approximately 384 randomized participants.

For Study A, conducted in the omalizumab naïve population, approximately 130 participants will be randomized. This corresponds to approximately 65 participants who will be randomly assigned to each intervention arm. It is planned that approximately 5% of participants enrolled will be adolescents and up to approximately 5% of participants enrolled will be children ≥6 to <12 years of age (both children and adolescents recruited in some selected countries). The actual number of participants randomized in Study A was 138.

For Study B, conducted in the omalizumab intolerant or incomplete responder population, approximately 104 participants were to be randomized. It was planned that approximately 5% of participants enrolled would be adolescents (recruited in some selected countries). The study recruitment ended, and the final number of participants randomized in Study B was 108. An interim analysis was performed when the first 83 randomized participants had completed their 24-week treatment period, by the interim analysis cut-off date, and met futility criteria. The study treatment is being stopped for the participants still on study treatment and all participants should complete their follow up period.

Omalizumab incomplete responders are defined as participants treated with at least 300 mg omalizumab every 4 weeks (q4w) for at least 3 months (minimum of 3 injections) and who have had an inadequate response resulting in omalizumab discontinuation, as confirmed by Investigator assessment.

For Study C, to be conducted in the omalizumab naïve population, approximately 150 participants will be randomized. This corresponds to approximately 75 participants who will be randomly assigned to each intervention arm. It is planned that approximately 5% of participants enrolled will be adolescents and up to approximately 5% of participants enrolled will be children ≥6 to <12 years of age (both children and adolescents recruited in some selected countries). In Study A, overall 52% of participants received H1-AH at recommended doses as background therapy, and 45% of participants presented with angioedema at baseline. To maintain consistency between the study population in studies A and C, and reflect the real-life distribution of patients with angioedema and uncontrolled by both standard dose or maximal H1-AH therapy, it is planned that

Study C would include not more than approximately 50% of participants (n=75) having their H1-AH therapy at recommended doses (for more details please see Section 6.1.2), and not less than approximately 30% (n=45) but not more than approximately 45% (n=68) of participants presenting with angioedema at baseline.

It is anticipated that approximately 30%-40% of enrolled participants will have angioedema.

Intervention groups and duration:

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

- Dupilumab:
  - Adults: 300 mg every 2 weeks (q2w)
  - Adolescents: 200 mg q2w for adolescents <60 kg at screening or 300 mg q2w for adolescents ≥60 kg at screening
  - Study A and Study C (only): Children ≥6 to <12 years of age: 200 mg q2w for children ≥30 kg at screening and 300 mg q4w for children <30 kg and ≥15 kg at screening
- 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 or
- 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:

- 1 injection q2w/q4w after an initial loading dose (2 injections) on Day 1

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:

- 1 injection q2w/q4w after an initial loading dose (2 injections) on Day 1

  Participants should continue their established standard of care background therapy with a long-acting non-sedating H1-AH, at up to 4-fold the recommended dose. If participants are on a dose higher than 4-fold the recommended dose at the screening visit (Visit 1), the Investigator can adjust the participant dose within the stipulated range at the screening visit (Visit 1). Participants should continue to take the same daily dose throughout the study unless they experience a flare for which rescue therapy may be initiated. Please refer to Section 6.5.1 for rescue therapy. The following list of H1-AH is allowed and noted with their recommended dose:
- Cetirizine 10 mg once per day (qd).
- Levocetirizine dihydrochloride 5 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-AH after discussion with the Sponsor

For other information related to H1-AH including safety precautions, please refer to the National 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-trial access to study medication

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

Statistical considerations:

Study A and Study C (omalizumab naïve); and Study B (omalizumab intolerant or incomplete responders) will all be analyzed separately and each tested at alpha level at 0.05. Integrated analyses may also be performed.

- **Sample size calculations**

  For Study A (omalizumab naïve): An effect size of 0.7 or higher is assumed. An absolute change of 5 in ISS7 score is considered the minimal clinically important difference (MCID) and an absolute change of 10 in UAS7 score is considered the MCID. Based upon an SD of 7, a change of 5 in the ISS7 would correspond to an effect size of approximately 0.7. Based upon an SD of 14, a change of 10 in the UAS7 would correspond to an effect size of approximately 0.7. Based on this assumption, plus the assumption of a 15% dropout rate and inclusion of children, it is estimated that 65 participants per group will provide 96% power to detect an effect size of 0.7 or higher between the dupilumab arm and placebo using a 2-sided t-test with alpha = 0.05. This sample size estimate applies to both ISS7 (primary endpoint for all countries except EU and EU reference countries) and UAS7 (primary endpoint for EU and EU reference countries).

  For Study B (omalizumab intolerant or incomplete responders): An effect size of 0.7 or higher is assumed. An absolute change of 5 in ISS7 score is considered the minimal clinically important difference (MCID) and an absolute change of 10 in UAS7 score is considered the MCID. Based upon an SD of 7, a change of 5 in the ISS7 would correspond to an effect size of approximately 0.7. Based upon an SD of 14, a change of 10 in the UAS7 would correspond to an effect size of approximately 0.7. Based on this assumption, plus the assumption of a 15% dropout rate, it is estimated that 52 participants per group will provide 90% power to detect an effect size of 0.7 or higher between the dupilumab arm and placebo using a 2-sided t-test with alpha = 0.05. This sample size estimate applies to both ISS7 (primary endpoint for all countries except EU and EU reference countries) and UAS7 (primary endpoint for EU and EU reference countries).

  Considering the reduced drop-out rate of 10% observed during the Study A, an interim analysis will be performed when the first 80 randomized participants would have completed their Week 24 visit by the interim analysis cut-off date. Using the O'Brien-Fleming approach with information fraction 0.77 and overall type-I error controlled at 0.05, the alpha spending at this interim analysis will be 0.021, and the alpha spending at the final analysis when all 104 participants complete the study will be 0.043.

  At the Study B interim analysis, it is estimated that 40 participants per group will provide 74% power to detect a treatment effect of 5 or higher with SD 7 and minimal detectable difference (MDD) of approximately 3.8 for ISS7 and a treatment effect of 10 or higher with SD 14 and MDD of approximately 7.6 for UAS7 between the dupilumab arm and placebo using a 2-sided t-test with alpha = 0.021.

  With the decision process outlined in Section 9.5, the overall power for the study will be approximately 88%.

  For Study C (omalizumab naïve): An effect size of 0.564 or higher is assumed. Based upon an SD of 7.5 (pooled SD from the observed data in Study A), a treatment difference of 4.23 in the ISS7 would correspond to an effect size of approximately 0.564. Based upon an SD of 14.3 (pooled SD from the observed data in Study A), a treatment difference of

8.53 in the UAS7 would correspond to an effect size of approximately 0.597. Based on this assumption, plus the assumption of a 10% dropout rate, it is estimated that 75 participants per group will provide 90% power to detect an effect size of 0.564 or higher between the dupilumab arm and placebo using a 2-sided t-test with alpha = 0.05. This sample size estimate applies to both ISS7 (primary endpoint for all countries except EU and EU reference countries) and UAS7 (primary endpoint for EU and EU reference countries).

The sample size calculations and the alpha spending by O'Brien-Fleming approach were calculated by nQuery Advisor and nTerim 4.0.

- **Randomization**

  Participants will be randomized into Study A (omalizumab naïve), Study B (omalizumab intolerant or incomplete responders), and Study C (omalizumab naïve) separately. For each study, patients will be randomized 1:1 to dupilumab or placebo. The randomization will be first stratified by age (adults versus adolescents versus children in Study A and Study C, adults versus adolescents in Study B; up to approximately 5% of total sample size for children and approximately 5% of total sample size for adolescents in Study A and Study C; up to approximately 5% of total sample size for adolescents in Study B). In adults, randomization will be stratified further by country (Study A, B and C) and presence of angioedema at baseline (Study C only). In adolescents/children ≥6 to <12 years of age, randomization will not be stratified further. In Study A, overall 52% of participants received H1-AH at recommended doses as background therapy, and 45% of participants presented with angioedema at baseline. To maintain consistency between the study population in studies A and C, and reflect the real-life distribution of patients with angioedema and uncontrolled by both standard dose or maximal H1-AH therapy, it is planned that Study C would include not more than approximately 50% (n=75) of participants having their H1-AH therapy at recommended doses (for more details please see Section 6.1.2), and not less than approximately 30% (n=45) but not more than approximately 45% (n=68) of participants presenting with angioedema at baseline.

- **Analysis population**

  Within each study, 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. For Study B interim analysis, the primary analysis population will be the intent-to-treat24 (ITT24) population, defined as all participants who were randomized at least 24 weeks before the interim analysis cut-off date and would have completed the Week 24 visit by the cut-off date of interim analysis.

  Within each study, 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 variable is change from baseline in ISS7 at Week 24 (except EU and EU reference countries).

  For EU and EU reference countries, the primary efficacy variable is change from baseline in UAS7 at Week 24.

  The following null hypothesis and alternative will be tested for dupilumab against placebo:

  - 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 a hybrid method of the worst-observation carried forward (WOCF) and multiple imputation. For participants taking selected prohibited medications and/or rescue medications (details of selection will be specified in the statistical analysis plan [SAP]), their data after the medication usage will be set to missing, and the worst postbaseline value on or before the time of the medication usage will be used to impute missing Week 24 value (for participants whose postbaseline values are all missing, the baseline will be used to impute). Participants who discontinue the treatment prematurely are encouraged to follow the planned clinical visits and in these participants, who did not take the selected prohibited medications and/or rescue medications, all data collected after 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 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 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 selected prohibited medications and/or 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 primary endpoint, treatment group, presence of angioedema at baseline, and region (combined countries) as covariates. Statistical inference obtained from all imputed data will be combined using Rubin's rule.

- **Analysis of secondary endpoints**

  Continuous endpoints will be analyzed using the same approach as the primary efficacy variable.

  Responder endpoints will be analyzed using the Cochran-Mantel-Haenszel (CMH) test adjusted by baseline disease severity, presence of angioedema at baseline, and regions. The baseline disease severity will be defined according to UAS7 <28 or ≥28. Comparisons of the response rates between dupilumab dose and placebo will be derived.

  Participants who receive selected prohibited medications and/or rescue medications will be considered as non-responders for time points after medication usage. For other patients, all available data including those collected during the off-treatment period will be used to determine the responder/non-responder status. Missing data will be considered as non-responders.

Time-to-event endpoints will be analyzed using the Cox proportional hazards model, including treatment, the corresponding baseline value, presence of angioedema at baseline, and region as covariates. The estimates of the hazard ratio between dupilumab dose and placebo will be derived.

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**

  The ISS7 score is the sum of the daily ISS scores over 7 days each week. When 1 or more of the daily ISS scores are missing, the following principles will be applied to handle the missing data:

  - Baseline ISS7 should not have missing daily ISS score which is guaranteed by the inclusion criteria (I 05).
  - For postbaseline ISS7, if a patient has at least 4 non-missing daily ISS scores within the 7 days of the calculated week, the ISS7 score is calculated as the sum of the available electronic diary (e-diary) ISS scores in the 7 days, divided by the number of days that have a non-missing diary ISS score, multiplied by 7.
  - For postbaseline ISS7, if there are less than 4 non-missing daily ISS scores within the 7 days of the calculated week, then the ISS7 score is missing for the week.

  The same principle will be applied to handle the missing data for all of the weekly outcomes including UAS7 and HSS7.

  For participants discontinuing the treatment before Week 24, off study-treatment values measured up to Week 24 will be included in the analysis. For participants taking selected prohibited medications and/or rescue medications, their data after the medication usage will be set to missing. For continuous endpoints, missing data will be imputed by the hybrid method of WOCF and multiple imputation as described above. 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**

  Within each study, Study A and Study C (omalizumab naïve), and Study B (omalizumab intolerant or incomplete responders), the multiplicity procedure is proposed to control the overall Type-I error rate for testing the primary endpoint and the key secondary endpoints. Detailed hierarchical testing procedure will be defined in the study SAP.

  Study A and Study C are each considered positive when the primary endpoint achieves statistical significance with 2-sided significance level 0.05.

  At the interim analysis, the study B is considered positive when the primary endpoint achieves statistical significance using 2-sided significance level 0.021. If Study B meets the criteria to continue at the interim analysis, at the final analysis of Study B, it will be considered positive when the primary endpoint achieves statistical significance using 2-sided significance level 0.043.

  Multiplicity adjustment for the other efficacy endpoints will be described in the study SAP.

- **Planned database lock date/interim analysis**

  The database locks will be implemented separately for Study A (omalizumab naïve), Study B (omalizumab intolerant or incomplete responders), and Study C (omalizumab naïve).

  Study A and Study C:

  A primary database lock for each study will be performed when all randomized participants have completed their 24-week treatment phase.

  The database for each study 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.

  Study B

  An interim analysis was performed for Study B when the defined ITT24 population data were available. The final database lock for study B will occur at the end of the study for all participants.

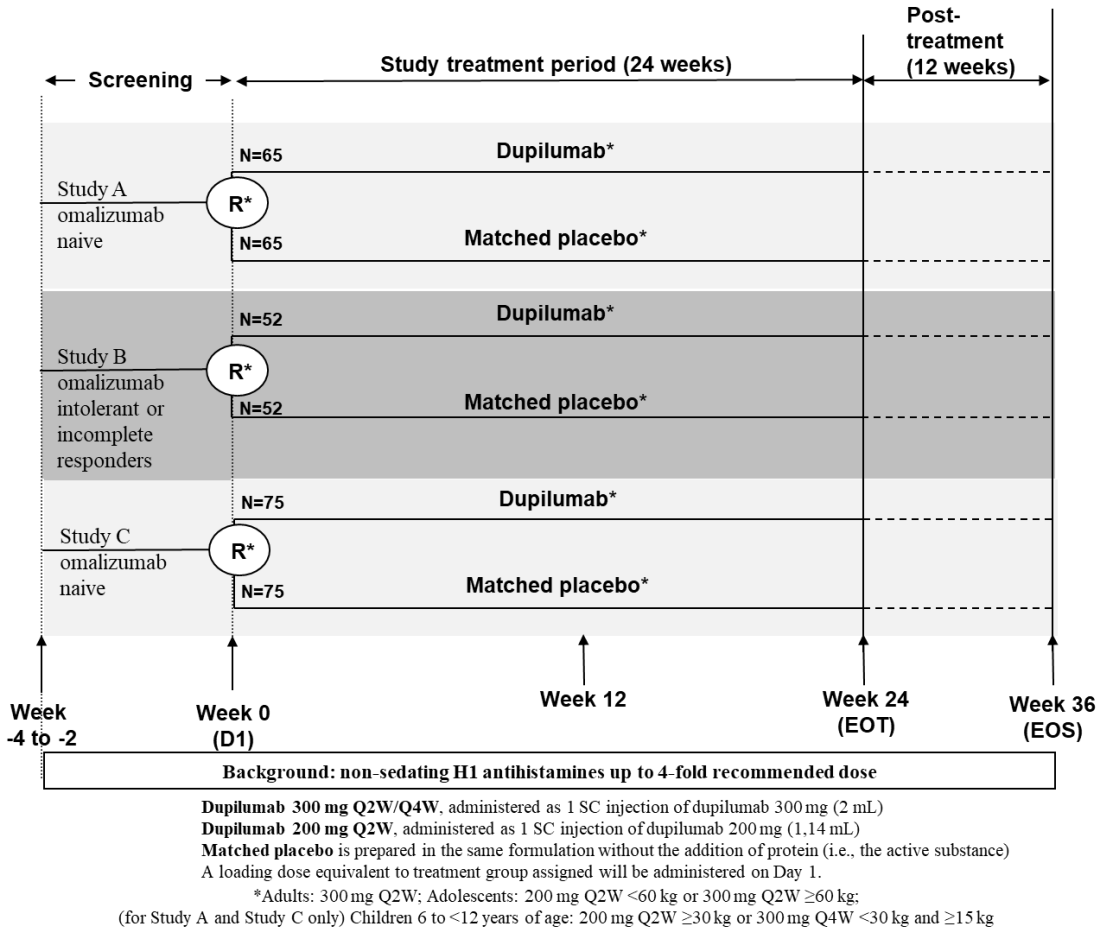
- **Unblinding plan**

  The detailed unblinding plan for the 3 studies, Study A and Study C (omalizumab naïve) and Study B (omalizumab intolerant or incomplete responders), will be included in the SAP or in a separate document.

Data Monitoring Committee: No

1.2 SCHEMA

Figure 1 - Graphical study design



Dupilumab 300 mg Q2W/Q4W, administered as 1 SC injection of dupilumab 300 mg (2 mL)
Dupilumab 200 mg Q2W, administered as 1 SC injection of dupilumab 200 mg (1,14 mL)
Matched placebo is prepared in the same formulation without the addition of protein (i.e., the active substance)
A loading dose equivalent to treatment group assigned will be administered on Day 1.
*Adults: 300 mg Q2W; Adolescents: 200 mg Q2W <60 kg or 300 mg Q2W ≥60 kg;
(for Study A and Study C only) Children 6 to <12 years of age: 200 mg Q2W ≥30 kg or 300 mg Q4W <30 kg and ≥15 kg

Abbreviations: EOS = End of study; EOT = End of treatment; R = randomization; SC = subcutaneous; Q2W = every 2 weeks; Q4W = every 4 weeks

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening (2 to 4 weeks before Day 1)	Intervention period (Weeks)			Follow-up (12 weeks)	Notes
		0 (Day 1)	12	24	36	Visit window: ±3 days for Visits 3, 4, and 5
Visit	**1**	**2**[a]	**3**	**4 (EOT)**[b]	**5 (EOS)**	
Screening/baseline:						
Informed consent	X					
Medical history	X					
Prior and concomitant medication	X	X	X	X	X	Concomitant medication including rescue OCS taken since last visit will be collected throughout the study
Demographics	X					
Inclusion/exclusion criteria	X	X				
Patient e-diary training	X	X				
Randomization		X				
Study intervention						
Call IVRS/IWRS	X	X	X	X	X	
IMP administration		X[c]				IMP will be administered every other week except (for study A and study C) for children <30 kg and ≥15 kg where it will be administered every 4 weeks. The planned last dose is at Week 22 except (for study A and study C) for children <30 kg and ≥15 kg where it will be administered at Week 20. Participants (or their care givers) are allowed to perform IMP injections at home.
Dispense/Upload electronic diary[d]	X	X				Device is dispensed at Screening (including instructions for use). At the EOS, the e-diary is returned to the site.
Safety[e]						
Physical examination[f]	X	X		X	X	
Vital signs[g]	X	X	X	X	X	
Electrocardiogram (12 lead)	X			X		ECG to be locally collected and read

Procedures	Screening (2 to 4 weeks before Day 1)	Intervention period (Weeks)			Follow-up (12 weeks)	Notes
		0 (Day 1)	12	24	36	Visit window: ±3 days for Visits 3, 4, and 5
Visit	**1**	**2**[a]	**3**	**4 (EOT)**[b]	**5 (EOS)**	
Hematology, biochemistry, urine analysis[h]	X	X	X	X	X	
Hepatitis, HIV Serology, TB test[i]	X					
Pregnancy test[j]	Serum	Ur	Ur	Ur	Ur	In between visit urine pregnancy tests must be performed at home (Weeks 4, 8, 16, 20, 28, and 32)
AE reporting, including SAEs	X	X	X	X	X	
Pharmacokinetics and ADA[e]						
Serum PK samples for dupilumab concentration[k]		X	X	X	X	
Anti-dupilumab antibody[k]		X	X	X	X	
Biomarkers[e]						
Serum total IgE		X	X	X	X	
Basophil activation test (optional sub-study)		X	X	X		For participants (except pediatric participants in Studies A and B and all Study C participants) who decide to participate and provide consent for the optional basophil activation test.
Skin biopsy (optional sub-study)		X		X		For participants (except pediatric participants) who decide to participate and provide consent for the optional skin biopsy. Two biopsies will be taken from each participant, 1 from lesion and 1 from non-lesion.
Archive serum and plasma samples (optional)		X	X	X	X	For participants (except pediatric participants) who decide to participate and 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.

Procedures	Screening (2 to 4 weeks before Day 1)	Intervention period (Weeks)			Follow-up (12 weeks)	Notes
		0 (Day 1)	12	24	36	Visit window: ±3 days for Visits 3, 4, and 5
Visit	**1**	**2**[a]	**3**	**4 (EOT)**[b]	**5 (EOS)**	
DNA (whole blood) samples - Optional		X				For participants (except pediatric participants) who decide to participate and provide 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.
RNA (whole blood) samples - Optional		X		X		For participants (except pediatric participants) who decide to participate and provide consent for the optional genomics sub-study (RNA sample collection). The RNA sample must be collected before the administration of the first dose of study drug and at Week 24 before the administration of study drug
Efficacy[d, e]						
UAS7	UAS7 (includes ISS7 and HSS7 as components), once daily from screening to EOS					To be recorded in e-diary on the same time of the day
AAS7	AAS7, once daily from screening to EOS					To be recorded in e-diary on the same time of the day
UCT		X	X	X	X	
DLQI/CDLQI		X	X	X	X	
CU-Q2oL		X	X	X	X	
PGIC			X	X		
PGIS	X	X	X	X		
EQ-5D-5L/EQ-5D-Y		X	X	X	X	
Missed school/work days[l]		X	X	X	X	

Procedures	Screening (2 to 4 weeks before Day 1)	Intervention period (Weeks)			Follow-up (12 weeks)	Notes
		0 (Day 1)	12	24	36	Visit window: ±3 days for Visits 3, 4, and 5
Visit	**1**	**2**[a]	**3**	**4 (EOT)**[b]	**5 (EOS)**	
Photographs CSU representative area for commercial activities (at selected sites in selected countries)		X	X	X	X	For participants (except pediatric participants in Studies A and B and all Study C participants) who decide to participate and provide consent for the photography, photographs will be taken of a representative area of CSU involvement for commercial activities. Instructions for taking the photographs are provided in the photography reference manual.

Abbreviations: AAS7 = angioedema activity score over 7 days; ADA = anti-drug antibodies; AE = adverse events; CDLQI = children's dermatology life quality index; CU-Q2oL = chronic urticaria quality of life questionnaire; DLQI = dermatology life quality index; DNA = deoxyribonucleic acid; ECG = electrocardiogram; eCRF = electronic Case Report Form; EOS = End of study; EOT = End of treatment; EQ-5D 5L = 5-level EuroQol 5-dimensional questionnaire; EQ-5D-Y = EuroQol 5-dimensional questionnaire youth; HBc Ab = hepatitis B core antibody; HBs Ab = hepatitis B surface antibody; HCV Ab = hepatitis C virus antibodies; HIV = Human Immunodeficiency Virus; HSS7 = hives severity score over 7 days; IgE = immunoglobulin E; IMP = investigational medicinal product; ISS7 = weekly itch severity score; IVRS = interactive voice response system; IWRS = interactive web response system; 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; UAS7 = urticaria activity score over 7 days; 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 subcutaneous (SC) injections.

b Participants who discontinue the study treatment prematurely (prior to completing the 24--week treatment period) will perform the EOT assessments at the time of discontinuation to assure a complete clinical assessment in close temporal proximity to the premature termination of study treatment In addition, to allow assessment of participant outcomes over the stipulated study period, participants will be asked and encouraged to complete all remaining study visits and participate in all assessments according to the visit schedule.

c Loading dose on Day 1 of 600 mg (2 SC injections of 300 mg) followed by 300 mg every 2 weeks (q2w) regimen for adults and adolescents ≥60 kg OR 400 mg (2 SC injections of 200 mg) followed by 200 mg q2w for adolescents <60 kg and children ≥30 kg (Study A and Study C) OR 600 mg (2 SC injections of 300 mg) followed by 300 mg q4w for children <30 kg and ≥15 kg (Study A and Study C) OR matched placebo.

d Electronic diary is used for daily recording of patient's answers to the urticaria activity score over 7 days (UAS7) and angioedema activity score over 7 days (AAS7) questionnaires as well as antihistamines medication use for the duration of the study. This device is dispensed at screening visit (Visit 1), including instructions for use. Electronic devices will be returned to the Sponsor after end of study (EOS). For urticaria control test (UCT), dermatology life quality index (DLQI [≥16 years old]) /children's dermatology life quality index (CDLQI [≥6 to <16 years old]), chronic urticaria quality of life questionnaire (CU-Q2oL), 5-level EuroQol 5-dimensional questionnaire (EQ-5D-5L [≥16 years old]) /EuroQol 5-dimensional questionnaire youth (EQ-5D-Y [≥6 to <16 years old]), patient global impression of change (PGIC), patient global impression of severity (PGIS), and missed school/work days questionnaires, the participant will fill in the questionnaires during their site visit on a tablet that will be provided to the site.

e Assessments/procedures should be conducted in the following order: participant-reported outcomes (other than participant assessment of injection pain), Investigator assessments, safety and laboratory assessments (including sample collection for anti-drug antibodies (ADA), pharmacokinetic (PK), biomarker, and optional DNA and RNA), and administration of study drug.

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

g Vital signs, including systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), axillary or oral temperature (same method of temperature measurement should be used during the course of the study) (°C), and respiratory rate will be measured at every visit in a semi-supine or sitting position after 5 minutes rest. Height (cm) will be measured at screening visit (Visit 1) only. Body weight (kg) will be measured at screening visit (Visit 1) and at end of treatment (EOT)/EOS Visits.

h 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, nitrate, 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 and macroscopic examination.

i Clinical laboratory testing at screening visit (Visit 1) will include hepatitis screen covering hepatitis B surface antigen (HBs Ag), hepatitis B surface antibody (HBs Ab), hepatitis B core antibody (HBc Ab), hepatitis C virus antibodies (HCV Ab), Human Immunodeficiency Virus (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. TB test will be performed locally if required and results noted in the eCRF.

j 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 site 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.

k 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.

l Baseline version to be administered at Baseline; post-Baseline version to be administered at the subsequent visits.

2 INTRODUCTION

Chronic spontaneous urticaria (CSU) is a common condition characterized by the spontaneous appearance of itchy wheals (hives) with or without angioedema persisting for more than 6 weeks without a specific known cause. Note that, CSU can also be referred to as chronic idiopathic urticaria (CIU). The underlying pathologic mechanism, while not well understood, is thought to be driven by mast cell activation and degranulation. Many symptoms of urticaria are mediated primarily by the actions of histamine (a mast cell mediator) on the H1-receptors, and treatment with H1-antihistamines (H1-AH) is a mainstay of therapy (1). Approximately 50% of patients achieve symptomatic control with conventional H1-AH therapy, defined as reduction of hives and itch to such an extent that UAS7 <6 (2). Some patients may remain symptomatic despite ongoing H1-antihistamine treatment. Omalizumab, a monoclonal anti-immunoglobulin E (IgE) antibody, has been approved for treatment for this group of patients. However, approximately a third of the patients, are not well-controlled by Week 12 following treatment with omalizumab, defined as persistent hives and itch, clinically validated as UAS7 >6 (3).

Dupilumab is a fully human monoclonal antibody (mAb) directed against the interleukin-4 receptor alpha (IL-4Rαs, 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 T helper 2 (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 inhibition of mast cell and basophil degranulation, and reduction of IgE serum levels and down-regulation of the Type 2 pathway may prevent or reverse the development of atopic diseases. 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, decrease in urinary LTE4 and PGDM suggest inhibition of mast cells activation and release of preformed mediators.

2.1 STUDY RATIONALE

Chronic spontaneous urticaria (CSU) patients with and without angioedema experience debilitating hives and pruritus secondary to mast cell and basophil dysregulation. Degranulation of these cell types by Fc gamma receptor (FcεRI) activation, through agonistic autoantibodies or cell surface-bound IgE cross-linked by antigen, release histamine and other pro-inflammatory mediators leading to local tissue edema and pruritus. While antihistamines are the mainstay of therapy, not all patients are controlled with antihistamines alone. Targeting IgE by omalizumab has been successful in treating CSU patients but not all patients are adequately responsive to this 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, 5). Therefore, blockade

of IL-4/IL-13 by dupilumab represents a novel therapeutic approach for CSU 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. This further supports the rationale to target aberrant IL-4/IL-13 signaling with dupilumab in patients with CSU. As this is a novel therapy that acts further upstream than IgE-targeted therapies, the clinical trials proposed here will test the efficacy of dupilumab in patients who have failed anti-histamines alone or who have failed both anti-histamines and omalizumab. Efficacy in patients who were intolerant to omalizumab will also be assessed. The master protocol EFC16461 will include 3 studies in CSU patients who remain symptomatic despite the use of H1-AH treatment - 2 studies will be in patients who are omalizumab naïve (Study A and Study C) and the third study in patients who are intolerant or incomplete responders to omalizumab (Study B). The selected dosing regimen is dupilumab 300 mg every 2 weeks (q2w) with a loading dose of 600 mg for adults; 300 mg q2w with a loading dose of 600 mg for adolescents ≥60 kg at screening OR 200 mg q2w with a loading dose of 400 mg for adolescents <60 kg at screening; and 200 mg q2w with a loading dose of 400 mg for children ≥6 to<12 years of age with weight ≥30 kg at screening OR 300 mg q4w with a loading dose of 600 mg for children ≥6 to <12 years of age with weight <30 kg and ≥15 kg at screening. This dose is expected to achieve concentrations in serum that saturate the IL-4/IL-13 receptor and hence it is expected to provide the maximum benefit and therefore to achieve the optimal benefit/risk ratio in this patient population.

LIBERTY-CSU CUPID Study A was completed and demonstrated that dupilumab at the above-mentioned dosing regimen is efficacious versus placebo in participants with CSU who remain symptomatic despite the use of H1 antihistamine (H1-AH) treatment (6). The trial included a total of 138 participants (132 adults, 4 adolescents and 2 children), with 68 participants in the placebo group and 70 participants in the dupilumab group.

At the end of the 24-week treatment period, dupilumab demonstrated clinically meaningful and statistically significant improvement versus placebo, across the key components of CSU. These components include itch, as measured by the primary endpoint Itch Severity Score over 7 days (ISS7, range 0-21) at week 24, and overall urticaria activity, as measured by the key secondary composite endpoint of Urticaria Activity Score over 7 days (UAS7, range 0-42) at week 24. For ISS7, which was the primary endpoint, the least squares mean change from baseline was -6 for placebo and -10.2 for dupilumab ($p < 0.001$), demonstrating that dupilumab treatment led to a statistically significant reduction in itch compared to placebo among participants with CSU. Similarly, for UAS7, the least squares mean change from baseline was -12 for placebo and -20.5 for dupilumab ($p<0.001$), demonstrating that dupilumab treatment also led to a statistically significant reduction in urticaria activity compared to placebo among patients with CSU.

Details are provided in Table 1 below.

Table 1 - Summary of the primary endpoints in Study A - ITT population

Parameter	Placebo[a] (N=68)	Dupilumab[a] (N=70)	Difference (95% CI)[b] for Dupilumab vs. Placebo	P-value
Primary endpoint for US and US ref. countries (key secondary endpoint for EU and EU ref countries)				
Change from baseline in ISS7 at Week 24	-6.01 (0.94)	-10.24 (0.91)	-4.23 (-6.63, -1.84)	**0.0005**
Primary endpoint for EU and EU ref. countries (key secondary endpoint for US and US ref countries)				
Change from baseline in UAS7 at Week 24	-12.00 (1.81)	-20.53 (1.76)	-8.53 (-13.16, -3.90)	**0.0003**

a Values presented are LS mean change from baseline

b Difference is LS mean difference

In regard to the safety endpoints, overall treatment-emergent adverse events reported in at least 5% of participants in any treatment group were comparable for placebo and dupilumab. A total of 58.8% of participants in the placebo group experienced any treatment-emergent adverse event, whereas 54.3% of participants in the dupilumab group experienced any treatment-emergent adverse event. Among the reported treatment-emergent adverse events, skin and subcutaneous tissue disorders were reported in 26.5% of participants in the placebo group and 14.3% of participants in the dupilumab group. These disorders included CSU in 8.8% of participants in the placebo group and 4.3% of participants in the dupilumab group. Additionally, 5 participants (7.4%) of the placebo group versus 1 participant (1.4%) of the dupilumab group experienced angioedema. The trial demonstrated safety results similar to the known safety profile of dupilumab in its approved indications.

Overall, in Study A dupilumab demonstrated clinically and statistically significant efficacy in patients with CSU who remain symptomatic despite the use of H1-AH treatment, as demonstrated by significantly reduced itch and hive severity and urticaria activity compared with standard of care H1-antihistamines alone. Dupilumab was well tolerated and demonstrated an acceptable safety profile in patients with CSU.

LIBERTY-CSU CUPID Study B evaluating dupilumab in participants with CSU who are intolerant or incomplete responders to omalizumab, has completed recruitment. Per protocol, a prespecified interim analysis for study B was performed. The outcome of this pre-specified interim analysis met the protocol efficacy statistical criteria for futility, with no new safety concerns identified. In Study B, the study treatment is being stopped for the participants still on study treatment. All participants should complete their follow up period.

Based on the positive results observed in the Study A in patients with CSU uncontrolled by antihistamine treatment, another study, LIBERTY-CSU CUPID Study C, will be conducted in the same population as Study A with a similar design to meet the Health Authority requirements to provide data from two adequate and well-controlled clinical trials to support filing of a marketing application.

2.2 BACKGROUND

Chronic spontaneous urticaria, formerly also known as chronic idiopathic urticaria and chronic urticaria, is 1 of the most frequent skin diseases. At any time, 0.5% to 1% of the population suffers from the disease (8). It is characterized by the spontaneous appearance of pruritic wheals (hives) and flare-type skin reactions persisting for more than 6 weeks without a specific known cause, which may be accompanied by angioedema. Although all age groups can be affected, the peak incidence is seen between 20 and 40 years of age. The duration of the disease is generally several years but is likely to be longer in more severe cases, cases with concurrent angioedema, in combination with physical urticaria or with a positive autologous serum skin test (auto-reactivity). Chronic spontaneous urticaria has major detrimental effects on quality-of-life, with sleep deprivation and psychiatric comorbidity being frequent. It also has a large impact on society in terms of direct and indirect health care costs as well as reduced performance at work and in private life (8).

In many patients, an underlying cause of CSU cannot be identified although release of histamine in the skin remains a common end-effector leading tot hives and angioedema. Therefore, the current treatment guidelines for the management of CSU recommend the use of non-sedating oral H1-AH as first-line therapy (9). In more than 50% of the patients, symptoms persist with standard dosing of antihistamines (8). Currently the only licensed treatment in antihistamine-refractory patients with CSU is omalizumab, a monoclonal anti-IgE antibody. In 2014, omalizumab was licensed for add-on therapy in CSU patients who still have symptoms despite standard-dosed antihistamine treatment (9). Omalizumab is highly effective in a large proportion of these patients (3, 10) and some patients with inducible urticaria (10). There is, however, still a great medical need for additional treatment options as 20% to 40% of patients are still without effective therapy.

In all 3 studies (A, B, and C), the target population consists of CSU patients who remain symptomatic despite treatment with H1-AH alone as these patients have a significant unmet medical need. The updated international guideline on the definition, classification, diagnosis and management of urticaria (1) provides evidence-based recommendations and a treatment algorithm. Steps 1 and 2 of this algorithm is the use of non-sedating H1-AHs at approved, or increased doses (up to 4-fold), respectively. Step 3 treatment options are omalizumab, ciclosporin A, or montelukast (LTRA). This master protocol allows the use of H1-AH at up to 4-fold the approved doses as background medication (Steps 1 and 2).

2.3 BENEFIT/RISK ASSESSMENT

Dupilumab has shown clinically relevant benefit in several Type 2-driven inflammatory disorders such as AD, asthma, and CRSwNP. A satisfactory safety profile has been observed so far in completed and currently ongoing studies in several other Type 2-mediated indications.

In asthma and AD indications, studies were also conducted in adolescents and similar efficacy as seen in adults has been observed. Data also showed similar efficacy, safety and PK between adult and adolescents. For AD and asthma, studies in pediatric participants (≥6 years and <12 years old) showed a similar efficacy, safety and PK profile compared with adults. Dupilumab was well tolerated in pediatric patients (ie, 6 to <18 years of age) with moderate to severe AD and with moderate-to-severe asthma.

Dupixent® (dupilumab) is authorized for marketing in over 60 countries worldwide including the US, European Union (EU) (Centralized Procedure), Japan, China, Canada, and Australia for the adult AD indication. Dupilumab is also authorized in the US, EU, and other jurisdictions for the pediatric (6 to <18 years of age) AD indications. Dupilumab is authorized for the asthma indication for the adult and pediatric patients (6 to <18 years of age) in the US and for adults and adolescents in the EU, Japan, and other jurisdictions. Dupilumab has also been approved for the CRSwNP indication in the US, EU, Japan, and other jurisdictions.

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 (4, 5, 11, 12, 13, 14). Unlike omalizumab, which specifically binds and inhibits IgE only, it is hypothesized that dupilumab will be effective in reducing itch and hives frequency/severity individual scores and composite, and improve angioedema and urticaria control as well as quality of life, in adults, adolescents, and children with CSU. Clinically validated measures, including the UAS7 score (which measures hive and itch severity over a 7-day period), its components consisting of the ISS7 (which measures itch severity over a 7-day period) and HSS7 (which measures hives severity over a 7-day period), the AAS7 (which measures the angioedema severity over a 7-day period, as well as health-related quality-of-life assessments will be assessed over a 24-week period (see details in Section 3.1). Supporting the mechanistic rationale for dupilumab's potential effectiveness in CSU as described in Section 2.1, dupilumab improved the hives and itch severity/frequency in a case series of 6 patients with CSU (4). An Investigator-initiated trial, currently ongoing, and this sponsor master protocol are the first 2 protocols studying dupilumab in patients with CSU to evaluate this hypothesis.

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 September 2021 (DLP), 13 062 participants were enrolled into the development program for dupilumab and were included in the safety population: 564 as healthy volunteers, 5011 from AD studies, 4091 from asthma studies, 782 from CRSwNP studies, 428 from EoE studies, 103 from the grass allergy study, 173 from peanut allergy studies, 1214 from the chronic obstructive pulmonary disease (COPD) studies, 309 from prurigo nodularis (PN) studies, and 235 from CSU studies, 30 from the chronic inducible cold urticaria (CICU) study, 16 from the chronic rhinosinusitis without nasal polyposis (CRSsNP) study, 34 from the bullous pemphigoid (BP) study, 22 from the allergic bronchopulmonary aspergillosis (ABPA) study, 42 from atopic hands and foot dermatitis (HFE) study, and eight from allergic fungal rhinosinusitis (AFRS) study. The number of participants exposed to dupilumab in clinical studies was 10 565 (538 in healthy volunteer studies, 4519 in AD studies, 3530 in asthma studies, 470 in CRSwNP studies, 378 in EoE studies, 52 in the grass allergy study, 124 in peanut allergy studies, 607 in COPD studies, 155 in PN studies, and 118 in the CSU studies, 15 in the CICU study, 8 in the CRSsNP study, 16 in the BP study, 10 in the ABPA study, 20 in the HFE study and 4 in the AFRS study.

Based on the sales figure retrieved from Margin Consolidated (MARCO) application 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 522 786 patient years (01 January 2017 through 30 September 2021).

Dupilumab was generally well tolerated in all populations tested in clinical development programs. The adverse drug reactions (ADRs) identified to date for dupilumab include injection site reactions, conjunctivitis, oral herpes, conjunctivitis allergic, conjunctivitis bacterial, herpes simplex, blepharitis, dry eye, eye pruritus, eosinophilia, and serum sickness. These ADRs were generally mild or moderate, transient, and manageable. These ADRs were not consistently observed in all indications (see Investigator's Brochure [IB] for greater details). More significant serious allergic reactions were very rare. 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 monoclonal antibodies 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 trials. Other potential risks based on the safety profile in particular indications are discussed in the IB. It is anticipated that dupilumab in patients with CSU will have a favorable safety profile as observed across other type 2-driven immunological disorders.

The safety data available to date, in conjunction with the risk monitoring and mitigation strategies in the study protocol, and the clinical benefit of dupilumab demonstrated in multiple Type 2 indications (AD, asthma, and CRSwNP) and a case series in CSU so far, support a favorable benefit-risk profile for dupilumab. Moreover, as described in Section 2.1 (Study Rationale), LIBERTY-CSU CUPID Study A safety results demonstrated that dupilumab was well tolerated and demonstrated an acceptable safety profile in patients with CSU who remain symptomatic despite the use of H1 antihistamine (H1-AH) treatment. In Study A, a total of 58.8% of participants in the placebo group experienced any treatment-emergent adverse event, whereas 54.3% of participants in the dupilumab group experienced any treatment-emergent adverse event. Treatment-emergent adverse events reported in at least 5% of participants in any treatment group were comparable for placebo and dupilumab. Among the reported treatment-emergent adverse events, skin and subcutaneous tissue disorders were reported in 26.5% of participants in the placebo group and 14.3% of participants in the dupilumab group. These disorders included CSU in 8.8% of participants in the placebo group and 4.3% of participants in the dupilumab group. Additionally, 5 participants (7.4%) of the placebo group versus 1 participant (1.4%) of the dupilumab group experienced angioedema. The trial demonstrated safety results similar to the known safety profile of dupilumab in its approved indications.

In addition, no new safety signal was identified in the LIBERTY-CSU CUPID Study B in participants with CSU who are intolerant or incomplete responders to omalizumab at the cut-off date for the pre-specified interim analysis.

A risk-benefit statement with respect to the overall development program is provided in the IB.

The rationale for the study design and justification for doses are detailed in Section 4.2 and Section 4.3, respectively.

3 OBJECTIVES AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To demonstrate the efficacy of dupilumab in study participants with CSU who remain symptomatic despite the use of H1-AH (Study A and Study C: omalizumab naïve; Study B: omalizumab intolerant or incomplete responders)	• Change from baseline in weekly itch severity score (ISS7) at Week 24 (except EU and EU reference countries) • For EU and EU reference countries only: Change from baseline in weekly urticaria activity score (UAS7, composite patient reported itch and hive score) at Week 24
Secondary	
• To demonstrate the efficacy of dupilumab on urticaria activity composite endpoint and itch or hives, separately, at various time points	• Change from baseline in weekly urticaria activity score (UAS7) at Week 12[a] and Week 24[b] (except EU and EU reference countries) • Change from baseline in ISS7 at Week 12[a] and at Week 24[b] (in EU and EU reference countries) • Change from baseline in weekly hives severity score (HSS7) at Week 12 and Week 24 • Time to ISS7 minimally important (MID) (ISS7 ≥5) response • Proportion of ISS7 MID (≥5 points) responders at Week 12[a] and Week 24[a] • Change from baseline in ISS7 at all time points (onset of action is assessed by the first p <0.05 that remains significant at subsequent measures until Week 24) • Proportion of patients with UAS7 ≤6 at Week 12[a] and Week 24[a] • Proportion of patients with UAS7 = 0 at Week 12[a] and Week 24[a]
• To demonstrate the efficacy of dupilumab on angioedema	• Change from baseline in angioedema activity score over 7 days (AAS7) at Week 12 and Week 24
• To demonstrate the efficacy of dupilumab on urticaria control	• Change from baseline in urticaria control test (UCT) at Week 12 and Week 24 • Proportion of well-controlled patients (UCT ≥12) at Week 12 and Week 24
• 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 patients ≥16 years old, and in Children's Dermatology Life Quality Index (CDLQI) in patients ≥6 to <16 years old at Week 12 and Week 24 • Patient Global Impression of Change (PGIC) of CSU at Week 12 and Week 24 • Change from baseline in Patient Global Impression of Severity (PGIS) of CSU at Week 12 and Week 24

Objectives	Endpoints
• To evaluate the ability of dupilumab in reducing the proportion of patients who require treatment with oral corticosteroids (OCS)	• Time-to-event and proportion of patients receiving OCS for CSU during the planned treatment period
• 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 anti-drug antibodies (ADA) against dupilumab over time
Tertiary/exploratory	
• To demonstrate exploratory outcome measures in the urticaria composite score and or its components	• Time to UAS7 MID response (9.5 to 10.5 points) by Week 12 and Week 24 • Change from baseline in the number of itch-free days and/or hive-free days at Week 12 and Week 24 • Change in UAS7 in well-controlled patients (UAS ≤6) from Weeks 24 to 36
• To demonstrate exploratory health-related quality-of-life and health status measures	• Change from baseline in EQ-5D-5L (or EQ-5D-Y 5L for ≥6 to <16 years old) at Week 12 and Week 24 • Change from baseline in CU-Q2oL at Week 12 and Week 24 • Missed school/work days from baseline at Week 12 and Week 24
• To demonstrate reduction in use of rescue medication	• Use of antihistamine rescue medication • Total OCS rescue dose prescribed (in mg) during the treatment period • Total OCS rescue intake in days during the treatment period
Pharmacokinetic • To evaluate PK and pharmacodynamic (PD) outcome measures	• Functional dupilumab concentrations in serum and PK profile • Pharmacodynamic response for selected biomarkers (total IgE)

a Key secondary endpoint for Study A and B
b Key secondary endpoint for Study C: UAS7 at Week 24 (except EU and EU reference countries, where ISS7 at Week 24 is key secondary endpoint)

3.1 APPROPRIATENESS OF MEASUREMENTS

The assessments used in this study are standard for the evaluation of therapy in participants with CSU. CSU is characterized by the recurrent formation of itchy hives, angioedema, or both for longer than 6 weeks (15, 16). The proposed primary endpoint is the change from baseline in weekly itch severity score (ISS7) at Week 24 (except EU and EU reference countries) and change from baseline in weekly urticaria activity score (UAS7, composite patient reported itch and hive score) at Week 24 for EU and EU reference countries. Itch is one of the most important patient relevant symptoms affecting quality of life in CSU and highly linked to how patients perceive their disease. ISS7 is one of the 2 components of urticaria activity score UAS7 (a composite score assessing both itch and hives) and an established and widely accepted patient-reported outcome tool to prospectively measure CSU activity (17) that has been used in most clinical trials in CSU in the recent years as a main outcome parameter (3, 18).

Angioedema has been described as a highly prevalent clinical feature in CSU. Up to 40% of CSU patients can present with a mixed phenotype of urticarial and angioedema and 10% with angioedema alone (19). Angioedema Activity Score (AAS) a well-developed and adequately validated instrument to measure angioedema activity in CSU patients (20) will thus be assessed to explore angioedema activity.

In addition to the UAS and angioedema, which provides a summary of signs and symptoms, it is important to get insights into patient self-assessment of disease control. To get a complete picture of the disease and assess its control over the course of treatment, a well-developed and validated instrument in CSU patients: the Urticaria Control Test will be used (21).

Lastly, patients with CSU experience substantial HRQoL impairment. Therefore, the dermatology life quality index (DLQI) or the children's dermatology life quality index (CDLQI), 2 instruments developed to measure dermatology-specific quality of life in adult and in pediatric patients, respectively (22, 23) will be assessed.

The proposed primary and secondary endpoints will answer important clinical questions about the efficacy on disease symptoms and quality of life (QoL) in patients with CSU.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a master protocol composed of 3 studies of similar design, 2 studies in participants who are omalizumab naïve (Study A and Study C) and 1 study in participants who are omalizumab intolerant or incomplete responders (Study B). The Study A and Study C will include adults, adolescents (≥12 to <18 years) and children (≥6 to <12 years in some selected countries). The study B will include adults and adolescents. The three studies are 24-week, double-blind, randomized, placebo-controlled studies to evaluate the use of dupilumab in participants with CSU who remain symptomatic despite the use of H1-AH.

Omalizumab incomplete responders are defined as patients treated with at least 300 mg omalizumab subcutaneous (SC) every 4 weeks (q4w) for at least 3 months (minimum of 3 injections) and who have had an inadequate response resulting in omalizumab discontinuation, as confirmed by Investigator assessment. Information about intolerance or incomplete response to omalizumab should be well documented in the patient´s medical records.

The total anticipated number of participants across the 3 studies is approximately 384 randomized participants. For each study, participants will be randomized 1:1 to dupilumab or placebo. The randomization will be stratified first by age (adults versus adolescents versus children in Study A and Study C, adults versus adolescents in Study B; up to approximately 5% of total sample size for children and approximately 5% of total sample size for adolescents in Study A and Study C; up to approximately 5% of total sample size for adolescents in Study B). In adults, randomization will be stratified further by country (Study A, B and C) and presence of angioedema at baseline (Study C only). In adolescents/children ≥6 to <12 years of age, randomization will not be stratified further.

It is anticipated that approximately 30%-40% of enrolled participants will have angioedema.

The studies will assess the effect of dupilumab on the itch and hives frequency/severity scored individually and through the urticaria activity score (composite), on angioedema activity, urticaria control, and on participants' HRQoL and health status.

Each of the 3 studies (A, B, and C) consists of 3 periods:

- Screening period (2 to 4 weeks).
- IMP treatment period (24 weeks ±3 days): approximately 384 participants (130 participants in Study A, 104 participants in Study B, and 150 participants in Study C) will be randomized (1:1) to 1 of the following treatments:
  - Dupilumab: 300 mg q2w for adults and adolescents ≥60 kg; 200 mg q2w for adolescents <60 kg and children ≥6 to <12 years of age ≥30 kg; or 300 mg q4w for children ≥6 to <12 years of age <30 kg and ≥15 kg (for Study A and Study C only).
  - Matched placebo.

  A loading dose equivalent to treatment group assigned will be administered on Day 1. Participants assigned to 300 mg q2w/q4w in dupilumab or matched placebo arm will

receive 2 injections of 2 mL on Day 1. Participants assigned to 200 mg q2w in dupilumab or matched placebo arm will receive 2 injections of 1.14 mL on Day 1.

- Post-IMP treatment period (12 weeks ±3 days).

In each of the 3 studies, participants should continue their established standard of care background therapy with a long-acting non-sedating H1-AH, at up to 4-fold the recommended dose. If participants are on a dose higher than 4-fold the recommended dose at screening visit (Visit 1), the Investigator can adjust the participant dose within the stipulated range at the screening visit (Visit 1). Participants should continue to take the same daily dose throughout the study unless they experience a flare for which rescue therapy may be initiated. All participants on 1- to 3-fold the approved H1-AH dose (maintenance dose used at screening) will be allowed to take additional doses of their H1-AH medications as rescue therapy as long as they do not exceed 4-fold the recommended dose during the screening, treatment, and follow-up periods. If symptoms are still uncontrolled after increase of H1-AH to the maximum allowed dose, participants can take a short course of OCS as rescue therapy during the treatment and follow-up periods. The participants who already take 4-fold an approved H1-AH dose will be allowed to take a short course of oral corticosteroids (OCS) as rescue therapy during the treatment and follow-up periods. For rescue therapy in participants in Japan, please see Appendix 11, Section 10.11. 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 each of the Studies A, B, and C, a randomized, placebo-controlled study design where the effect of the IMP is assessed in CSU patients with moderate to severe symptoms on top of optimized background therapy is considered to be the most appropriate design to explore the efficacy and safety of dupilumab in participants with CSU who remain symptomatic despite the use of H1-AH and who are omalizumab naïve or intolerant or incomplete responders.

Study A and Study C will target omalizumab naïve patients; more than 50% of CSU patients do not respond to H1 antihistamine treatment (1, 9). In Study A, overall 52% of participants received H1-AH at recommended doses as background therapy and 45% of participants presented with angioedema at baseline. In order to maintain consistency between the study population in studies A and C, and reflect the real-life distribution of patients with angioedema and uncontrolled by both standard dose or maximal H1-AH therapy, it is planned that Study C would include not more than approximately 50% (n=75) of participants having their H1-AH therapy at recommended doses (for more details please see Section 6.1.2), and not less than approximately 30% (n=45) but not more than approximately 45% (n=68) of participants presenting with angioedema at baseline.

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.

Study B will target omalizumab treated CSU patients. Approximately 20% to 40% patients don't respond to omalizumab and remain without an effective third-line treatment; these patients have the highest unmet medical need (1). Studies suggests that omalizumab incomplete or

non-responder patients had significantly lower baseline serum IgE levels compared to partial and complete responders (24, 25). 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 proinflammatory cytokines, chemokines, nitric oxide, and IgE (13). Elevated levels of IL-4 and IL-13 in the skin of CSU patients have been reported (26) and IgE levels are suppressed by inhibition of the cytokine IL-4. The study will also target omalizumab intolerant patients. Similar study designs and endpoints have been employed for recent studies with other biologics and are considered "state-of-the-art" for studies in CSU (10).

Including approximately 5% of adolescent patients in each study is consistent with the omalizumab clinical development program and approximates the prevalence of adolescent patients with CSU (9).

The 24-week treatment duration should be sufficient for proving efficacy of dupilumab. Dupilumab treatment has shown clinical efficacy prior to Week 24 in all other Phase 3 trials 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 atopic dermatitis trials, including the 52-week atopic dermatitis 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 chronic spontaneous urticaria. Study A was completed, and results confirm that 24-week treatment is an appropriate duration to evaluate dupilumab impact on efficacy in participants with CSU. 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.

Moreover, Study A demonstrated that the proposed dupilumab dosing regimen was efficacious versus placebo in omalizumab-naïve patients with CSU who remain symptomatic despite the use of H1 antihistamine (H1-AH) treatment (please see Section 2.1 for more details on study results).

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, Efficacy will be determined using the primary endpoint of the change from baseline in the weekly itch severity score (ISS7) at Week 24 (except EU and EU reference countries) and change from baseline in weekly urticaria activity score (UAS7, composite patient reported itch and hive score) at Week 24 for EU and EU reference countries. Assessment of itch is important as it is the key symptom affecting participants´ QoL.

4.3 JUSTIFICATION FOR DOSE

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 OR 200 mg q2w with a loading dose of 400 mg for adolescents <60 kg. These are the approved dose regimens for AD, another skin disease. The doses proposed for children ≥6 to <12 years of age are the dose regimens for the same age for AD, which have been submitted to the Health Authorities and are currently in review: 200 mg q2w with a loading dose of 400 mg for children ≥6 to <12 years of age with weight ≥30 kg or 300 mg q4w with a loading dose of 600 mg for children ≥6 to <12 years of age with weight <30 kg and ≥15 kg. The proposed doses are expected to achieve concentrations in serum that saturate the IL4/13 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 CSU 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 pharmacodynamics (PD) response as demonstrated by improvement in pruritus, a hallmark of AD. Similarly, as pruritus is a core symptom of CSU, and to achieve effective drug concentrations more rapidly, a loading dose is selected for this study.

EFC16461 Study A (n=138) conducted in adults, adolescents and children ages 6-11 years with CSU who remain symptomatic despite the use of H1 antihistamine (H1-AH) treatment demonstrated that dupilumab at dose regimens described above provide clinically meaningful and statistically significant improvement versus placebo, across the key symptoms of CSU (including itch, hives and overall urticaria activity) at Week 24 and is well tolerated in the studies population.

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 end of study (EOS) Visit. If a participant discontinues 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

For each of the 3 Studies A, B, and C, participants are eligible to be included in the study only if all of the following criteria apply:

Age

I 01. Study A and C: Participant must be ≥6 years to 80 years of age at the time of signing the informed consent.

Study B: Participant must be ≥12 years (or the minimum legal age for adolescents in the country of the investigational site) to 80 years of age at the time of signing the informed consent

Note: For those countries where local regulations do not permit enrollment of children aged ≥6 to <12 years, the recruitment will be restricted to those who are ≥12 years of age (or the minimum legal age for adolescents in the country of the investigational site). For those countries where local regulations do not permit enrollment of children aged ≥6 to <12 years of age and adolescents, the recruitment will be restricted to those who are ≥18 years of age. See instructions specific to France in Appendix 11 (Section 10.11.2).

Type of participant and disease characteristics

Participants who have a diagnosis of CSU refractory to H1-AH at the time of randomization, as defined by all of the following:

I 02. Diagnosis of CSU >6 months prior to screening visit (Visit 1).

I 03. The presence of itch and hives for >6 consecutive weeks at any time prior to screening visit (Visit 1) despite the use of H1-AH during this time period.

I 04. Participants using a study defined H1-AH for CSU treatment (see Section 6.1.2 for the list of antihistamines allowed for the study). Note: Participants should remain on their prescreening non-sedating H1-AH dose. Only up to 4-fold the recommended dose is allowed. If participants are on dose higher than 4-fold the recommended dose at screening, the Investigator can adjust the participant dose to the stipulated range at the screening visit (Visit 1). The H1-AH dose should be stable for at least 3 consecutive days prior to the screening visit (Visit 1).

I 05. During the 7 days before randomization:

- UAS7 ≥16
- ISS7 ≥8

Note: To be eligible for the study, participants must have no missing electronic diary (e-diary) (UAS7 and ISS7) in the 7 days before randomization.

I 06. Deleted in Amended protocol 02.

I 07. Study A and C (omalizumab naïve): Participants who are omalizumab naïve.

Study B (omalizumab intolerant or incomplete responders): Omalizumab incomplete responders are defined as participants treated with at least 300 mg (q4w) omalizumab for at least 3 months (minimum of 3 injections) and who have had an inadequate response resulting in omalizumab discontinuation, as confirmed by Investigator assessment.
Note: Information about intolerance or incomplete response to omalizumab should be well documented in the patient´s medical records.

I 08. Participants must be willing and able to complete a daily symptom e-diary for the duration of the study.

Sex

I 09. 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 an acceptable contraceptive method as described in Appendix 4 (Section 10.4) during the study (at a minimum until 12 weeks after the last dose of study intervention).
  - A WOCBP must have a negative highly sensitive (Section 10.2) 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).
- 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

I10. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1) of the protocol which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Participants ≥6 and <18 years of age must provide written informed assent, and their parent(s)/caregiver(s)/legally authorized representative(s) must sign the specific ICF. In countries where legal age of majority is >18 years, a specific ICF must also be signed by the participant's legally authorized representative (Section 10.1.3).

5.2 EXCLUSION CRITERIA

For each of the 3 studies A, B, and C, participants are excluded from the study if any of the following criteria apply:

E 01. Weight is less than 30 kg in adults and adolescents and 15 kg in children aged ≥6 to <12 years

Medical conditions

E 02. Clearly defined underlying etiology for CUs other than CSU (main manifestation being physical urticaria). This includes but not limited to the following urticarias:
- Inducible urticaria: acute urticaria, solar, cholinergic, heat, cold, 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 03. Presence of skin morbidities other than CSU that may interfere with the assessment of the study outcomes.

E 04. Patients with active AD.

E 05. Severe concomitant illness(es) that, in the Investigator's judgment, would adversely affect the patient'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 [CRF], etc).

E 06. Patients with active tuberculosis (TB) or non-tuberculous 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 07. 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 08. 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 09. Known or suspected immunodeficiency, including history of invasive opportunistic infections (eg, 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 10. Active malignancy or history of malignancy within 5 years before the Baseline Visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin.

E 11. History of systemic hypersensitivity or anaphylaxis to omalizumab or any biologic therapy, including any excipients.

E 12. Patient with any other medical or psychological condition including relevant laboratory or electrocardiogram abnormalities at screening that, in the opinion of the Investigator, suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study participant as a result of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments. The specific justification for participants excluded under this criterion will be noted in study documents (chart notes, CRF, etc).

E 13. Current history of substance and/or alcohol abuse.

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

Prior/concomitant therapy

E 15. Exposure to another systemic or topical investigative drug (monoclonal antibodies 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 monoclonal antibodies, whichever is longer, and an interval of <30 days or <5 PK half-lives, whichever is longer, for investigative small molecules.

E 16. 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 17. Treatment with biologics as follows:
- Any cell-depleting agents including but not limited to rituximab: within 6 months before the screening visit (Visit 1).
- Omalizumab within 4 months before the screening visit (Visit 1).
- Other monoclonal antibodies (which are biological response modifiers): within 5 half-lives (if known) or 16 weeks before the screening visit (Visit 1), whichever is longer.

E 18. Treatment with a live (attenuated) vaccine (Section 10.10) 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:
- Patient for whom administration of live (attenuated) vaccine can be safely postponed would be eligible to enroll into the study.
- Patients who have their vaccination preponed can enroll in the study only after a gap of 4 weeks following administration of the vaccine.

E 19. Routine (daily or every other day during 5 or more consecutive days) doses of doxepin within 14 days prior to screening visit (Visit 1).

E 20. Either intravenous immunoglobulin (IVIG) therapy and/or plasmapheresis within 30 days prior to screening visit (Visit 1).

E 21. Planned or anticipated use of any prohibited medications (Section 6.5) and procedures during screening and study treatment period.

Prior/concurrent clinical study experience

E 22. Participation in prior dupilumab clinical study, or have been treated with commercially available dupilumab.

Diagnostic assessments

E 23. History of human immunodeficiency virus (HIV) infection or positive HIV 1/2 serology at the screening visit (Visit 1).

E 24. Patients with any of the following result at the screening visit (Visit 1):
- Positive (or indeterminate) HBs Ag or,
- Positive total HBc Ab confirmed by positive HBV DNA or,
- Positive HCV Ab confirmed by positive HCV RNA.

Other exclusions

E 25. Individuals accommodated in an institution because of regulatory or legal order; prisoners or subjects who are legally institutionalized.

E 26. Any country-related specific regulation that would prevent the subject from entering the study - see Section 10.11 (country-specific requirements).

E 27. Participant not suitable for participation, whatever the reason, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 28. Participants are dependent on the Sponsor or Investigator (in conjunction with Section 1.61 of the International Council for Harmonisation [ICH] - Good Clinical Practice [GCP] Ordinance E6).

E 29. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals.

E 30. Any specific situation during study implementation/course that may rise ethics considerations.

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

Not applicable.

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 serious adverse event (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).

There is no requirement for a waiting period between the screen failure date and the rescreening date. The Interactive Response Technology (IRT) report will flag rescreened participants. Patients that are rescreened must sign a new consent form and all Visit 1 procedures must be repeated.

If certain dynamic laboratory tests do not meet the eligibility criteria at the screening visit (Visit 1), these laboratory assessments may be repeated, at the discretion of the Investigator, if it is judged to be likely to return to acceptable range for study inclusion within the screening window prior to Day 1. There is no need to screen fail such participants if the test finally meets the eligibility criteria.

6 STUDY INTERVENTION

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

6.1 STUDY INTERVENTION(S) ADMINISTERED

6.1.1 Investigational medicinal product(s)

Table 3 - Overview of study interventions administered

ARM name	Dupilumab	Placebo
Intervention name	For adults and adolescents ≥60 kg: Dupilumab 300 mg (q2w) For adolescents <60 kg and children ≥6 to <12 years of age ≥30 kg: Dupilumab 200 mg (q2w) For children ≥6 to <12 years of age <30 kg and ≥15 kg: Dupilumab 300 mg (q4w)	For adults and adolescents ≥60 kg: Placebo matching dupilumab 300 mg (q2w) For adolescents <60 kg and children ≥6 to <12 years of age ≥30 kg: Placebo matching dupilumab 200 mg (q2w) For children ≥6 to <12 years of age <30 kg and ≥15 kg: Placebo matching dupilumab 300 mg (q4w)
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 or 300 mg every 28 ±3 days after an initial loading dose of 600 mg	0 mg every 14 ±3 days or 28 ±3 days after an initial loading dose of 0 mg
Route of administration	Subcutaneous	Subcutaneous
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 patient 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 patient kit box. Both glass pre-filled syringe and box will be labeled as required per country requirement

Between the protocol-scheduled on-site visits, interim visits may be required for IMP dispensing.

During the 24-week treatment period, the investigational medicinal product (IMP) is administered every 14 ±3 days (q2w) or 28 ±3 days (q4W) for children <30 kg and ≥15 kg.

The Investigator or delegate will train the participant (or parent(s)/legally authorized representative/caregiver) how to prepare and inject IMP at Visit 2. The site staff will inject the first dose of the 2 injections. The participant (or parent/legally authorized representative/caregiver) will perform the second injection under the supervision of the Investigator or delegate. This training must be documented in the participant's study file. At subsequent study drug administrations, participants are allowed to self-inject IMP at home. For children ≥6 to <12 years, no self-administration of IMP is allowed by the participant, but parent(s)/caregiver(s)/legally authorized representative(s) who are trained by the Investigator or designee to prepare and administer IMP may perform home administration of IMP.

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 site-specific requirements.

If the participant (or parent/legally authorized representative/caregiver) is unable or unwilling to administer IMP, injections can be performed at the site by way of unscheduled visits; or arrangements can be made for qualified site personnel and/or health care professionals (eg, visiting nurse service) to administer IMP for the doses that are not scheduled to be given at the study site.

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 Investigator or Delegate) or health care professional but not the participants themselves. The IMP injection should be avoided in areas where participants have urticaria or angioedema.

Participant/parent/legally authorized representative/caregiver should be trained by the site 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 site-specific requirements) following injection. In case of hypersensitivity symptoms the participant should contact healthcare provider/emergency.

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

6.1.2 Noninvestigational medicinal product(s)

Participants should continue their established standard of care background therapy with a long-acting non-sedating H1-AH, at up to 4-fold the recommended dose. If participants are on a dose higher than 4-fold the recommended dose at the screening visit (Visit 1), the Investigator can adjust the participant dose within the stipulated range at the screening visit (Visit 1). Participants should continue to take the same daily dose throughout the study unless they experience a flare for which rescue therapy may be initiated. Please refer to Section 6.5.1 for rescue therapy. The following list of H1-AH is allowed and noted with their recommended dose:

- Cetirizine 10 mg once per day (qd).
- Levocetirizine dihydrochloride 5 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-AH after discussion with the Sponsor

For other information related to H1-AH including safety precautions, please refer to the National 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.

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 study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention 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 site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention 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 8.3.7). 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 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 trial 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 study intervention using an IRT. The Investigator will be questioned during interactive voice response system (IVRS) phone call/interactive web response system (IWRS) web module if he/she wishes to enroll the patient in Study A or Study C, or Study B. 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 screening visit (Visit 1), the Investigator or designee will contact the IRT system to receive the participant number. If a patient who had previously failed screening is approached for rescreening, a new ICF must be signed. In such case, a new patient number will be assigned by IRT.

Methods of assigning patients 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 described in Table 3.

The randomization will be stratified first by age (adults versus adolescents versus children in Study A and Study C and adults versus adolescents in Study B; up to approximately 5% of total sample size for children and approximately 5% of total sample size for adolescents in Study A and Study C; up to approximately 5% of total sample size for adolescents in Study B). In adults, randomization will be stratified further by country (Study A, B and C) and presence of angioedema at baseline (Study C only). In adolescents/children ≥6 to <12 years of age, randomization will not be stratified further. In Study A, overall 52% of participants received H1-AH at recommended doses as background therapy, and 45% of participants presented with angioedema at baseline. To maintain consistency between the study population in studies A and C, and reflect the real-life distribution of patients with angioedema and uncontrolled by both standard dose or maximal H1-AH therapy, it is planned that Study C would include not more than

approximately 50% (n=75) of participants having their H1-AH therapy at recommended doses (for more details please see Section 6.1.2), and not less than approximately 30% (n=45) but not more than approximately 45% (n=68) of participants presenting with angioedema at baseline.

It is anticipated that approximately 30%-40% of enrolled participants will have angioedema.

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

Investigational medicinal products will be dispensed at the study visits summarized in the Schedule of activities (SoA).

Returned IMP 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 box will be labeled with a treatment kit number. While these are double-blind trials with regard to the treatment with either dupilumab or placebo, they are 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 and children ≥6 to <12 years of age. In addition, in children, the study is not blinded to dose regimen due to the different frequency of IMP administration (q4w versus q2w).

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 treatment 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 treatment assignment unless this could delay emergency treatment for the participant. If a participant's treatment assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

6.4 STUDY INTERVENTION COMPLIANCE

- Investigator or his/her delegate must ensure that IMP will be administered to each participant according to the labeling instructions.
- IMPs accountability:
  - IMPs 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 IMP accountability and inventory forms.

- The Investigator or his/her delegate records the dosing information on the appropriate pages of the electronic case report form (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 source documents.
- Paper diary will be dispensed to the participants for indicating the IMP administration at home.

Participant compliance with study intervention will be assessed at each visit. Compliance will be assessed by kit/pre-filled syringe. Deviation(s) from the prescribed dosage regimen should 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.

Long-acting non-sedating H1-AH, at up to 4-fold the recommended dose, are allowed as background medication and on demand as recue medication (for rescue therapy in participants in Japan, please see Appendix 11 Section 10.11). 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)
- Antifibrinolytic tranexamic acid and epsilon-aminocaproic acid
- Other monoclonal antibodies (which are biological response modifiers)
- Phototherapy, including tanning beds
- 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 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 CSU.

6.5.1 Rescue medicine

All participants on 1- to 3-fold the approved non-sedating H1-AH dose (maintenance dose used at screening) will be allowed to take additional doses of their H1-AH medications as rescue therapy as long as they do not exceed 4-fold the recommended dose during the screening, treatment, and follow-up periods. If symptoms are still uncontrolled after increase of H1-AH to the maximum allowed dose, participants can take a short course of OCS as rescue therapy during the treatment and follow-up periods. The participants on stable dose of 4-fold the approved H1-AH dose will be allowed to take a short course of OCS as rescue therapy 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.

For rescue medication in participants in Japan, please see Appendix 11 (Section 10.11).

The initial maintenance antihistamine dose should remain stable throughout the study, and participants should continue their maintenance dose once rescue treatment is no longer required.

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-AH and OCS including safety precautions please refer to the National 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 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 10.8).
- 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 10.9).
- 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).

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.

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 site 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.

7.1.2 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs.

In addition, if participants 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.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his/her own request, or if his/her parent(s)/caregiver(s)/legally authorized representative(s) decide to do so, 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 site study records.

If participants, or their parent(s)/caregiver(s)/legally authorized representative(s) wish to withdraw consent for participation into the study, the participants 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.

The participants who withdraw from the study intervention should be explicitly asked (or their parent(s)/caregiver(s)/legally authorized representative(s)) 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 site 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 site 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 assessments and procedures described below are common to Study A, Study B, and Study C.

- 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).
- Patient-Reported Outcome (PRO) questionnaires 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.
- Adolescents/children completing the questionnaires (UAS, AAS, UCT, Chronic Urticaria Quality of Life Questionnaire [CU-Q2oL], 5-level EuroQol 5 dimensional questionnaire [EQ-5D-5L] [≥16 years old], EuroQol 5-dimensional questionnaire youth [EQ-5D-Y] [≥6 to <16 years old], PGIS, PGIC, CDLQI [≥6 to <16 years old] and DLQI [≥16 years old]) 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. Adolescents and children should answer the question themselves; parents/caregivers should not influence nor interpret their child's answer. Parent(s)/caregiver(s)/ legally authorized representative(s) 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 168 mL. The maximum amount of blood collected expected as per schedule of activities from each adolescent over the duration of the study will not exceed 101 mL. The maximum amount of blood collected from each child will be compliant with the European guideline (27). The maximum amount of blood collected per each visit from each child aged ≥6 to <12 years will not exceed 11 mL per visit and the total maximum amount of blood collected expected as per schedule of activities for each child over the duration of the study will not exceed 47 mL. 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 (Coronavirus disease 2019) (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.

8.1 EFFICACY ASSESSMENTS

Efficacy data will be collected via electronic devices.

The e-diary is used for daily recording of PRO such as the UAS7 and AAS7 questionnaires, and use of H1-AH medication. This device will be dispensed at screening visit (Visit 1), including instructions for use and participant(s)/parent(s)/caregiver(s)/legally authorized representative(s) will be instructed on the use of the device.

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

On regular basis, the site staff should review on vendor´s website the information downloaded from participants´ e-diary. They should particularly check status of the disease reviewing UAS7 and AAS7, as well as compliance to background therapy and overall e-diary compliance. The site should follow-up with the subject as appropriate.

The same questionnaires as for adolescents aged <16 years will be used for children aged ≥6 to <12 years.

For UCT, DLQI (≥16 years old)/CDLQI (≥6 to <16 years old), CU-Q2oL, 5-level EuroQol 5-dimensional questionnaire (EQ-5D-5L) (≥16 years old)/EuroQol 5-dimensional questionnaire youth (EQ-5D-Y) (≥6 to <16 years old), PGIC, PGIS, and missed school/work days questionnaires, participant(s) will fill in the questionnaires during their site visit on a tablet that will be provided to the site. This device is kept at the site during the study.

8.1.1 Urticaria activity score

The Urticaria Activity Score (UAS) is a validated PRO measure. The daily UAS is the sum of the daily Hive Severity Score (HSS, ranging from 0 = None to 3 = more than 50 hives) and the daily Itch Severity Score (ISS, ranging from 0 = None to 3 = intense), the 2 key urticaria signs and symptoms which are wheals and itch. The daily UAS scores range from 0 to 6 point/day. Daily UAS scores are summed over 7-day period to create the UAS7, ranging from 0 to 42, and is composed of the HSS7 and ISS7 components. The UAS7 is an established and widely accepted

PRO tool to prospectively measure CSU activity (28). It has been used in most clinical trials in CSU in the recent years as a main outcome parameter and medical practice (3, 18). A minimal important difference (MID) value ranging from 9.5 to 10.5 has been defined to help interpretation of the change in score in CSU participants (29, 30, 31).

Participants will complete the UAS as described in the SoA (Section 1.3). The assessment tool is provided in Section 10.7.1.

8.1.2 Angioedema activity score

The Angioedema Activity Score (AAS) is a validated PRO measure that assesses angioedema activity (20). The AAS is a diary in which participants document on a daily basis the presence or absence of angioedema during the past 24 hours. If angioedema is present, participants answer 5 additional questions about the time of the day the swelling episode occurred, and the severity and impact on daily functioning and appearance this swelling episode has had. Each AAS item is scored between 0 and 3 points, that is, the minimum and maximum daily AASs are 0 and 15 points. The daily AASs are summed up to 7-day scores (AAS7), with 7-day scores ranging from 0 to 105 (20). A MID of the AAS7 of around 8 points has been established (20).

Participants will complete the AAS as described in the SoA (Section 1.3). The assessment tool is provided in Section 10.7.2.

8.1.3 Urticaria control test

The Urticaria Control Test (UCT) is a validated PRO measure for assessing urticaria control (20) based on 4 items (severity of pruritus and wheals urticaria symptoms; frequency of treatment being not sufficient; QoL impairment; overall urticarial control). Each item is rated on a 5-point Likert-type 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 points indicating complete disease control (20).

Participants will complete the UCT as described in the SoA. The assessment tool is provided in Section 10.7.3.

8.1.4 Dermatology life quality index and children's dermatology quality life quality index

The DLQI is a PRO developed to measure dermatology-specific HRQoL in adult participants (22). The instrument comprises 10 items assessing the impact of skin disease on participants' 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). 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).

The Children's Dermatology Quality Life Quality Index (CDLQI) is a validated questionnaire designed to measure the impact of skin disease on children's HRQoL (23). 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 (≥6 to <16 years old) as described in the SoA (Section 1.3). The assessment tools are provided in Section 10.7.4 and Section 10.7.5.

8.1.5 Chronic urticaria quality of life questionnaire

The CU-Q2oL is a disease-specific instrument used to assess the QoL in adult participants with CSU (34). The CU-Q2oL is a 23-item, self-administered questionnaire that includes 6 QoL dimensions: pruritus, swelling, impact on life activities, sleep problems, limits, and looks. Each item is scored on a 5-point Likert scale (1 = not at all, 5 = extremely) where participants indicate how troubled they are within each dimension. The individual items are summed to generate the overall CU-Q2oL score, which is then converted to a 0 to 100 scale; higher scores indicate greater QoL impairment.

Participants will complete the CU-Q2oL as described in the SoA (Section 1.3). The assessment tool is provided in Section 10.7.6.

8.1.6 Patient Global Impression of Change of CSU disease and Patient Global Impression of Severity of CSU disease

The Patient Global Impression of Change (PGIC) is a 1-item questionnaire that asks the participant to provide the overall self-assessment of change in their CSU on a 7-point scale, compared to 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 Patient Global Impression of Severity (PGIS) is a 1-item questionnaire that asks participants to provide the overall self-assessment of their participant' disease severity on a 4-point scale for the past week. Response choices are: 1 = "none", 2 = "Mild", 3 = "Moderate", 4 = "Severe".

Participants will complete the 2 items as described in the SoA (Section 1.3). The items are provided in Section 10.7.7 and Section 10.7.8.

8.1.7 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 adult version of the questionnaire is adapted to patients aged 16 and older. The EQ-5D consists of 2 parts: the descriptive system and the EQ 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 inability to do the activity (35). 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, VAS 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 EQ-5D Youth version (EQ-5D Y) will be administered to children ≥6 to <12 years old and adolescents 12 to 15 years old (36). The EQ-5D-Y is based on the EQ-5D-3L and essentially consists of 2 pages: the EQ-5D descriptive system and the EQ VAS. The EQ-5D-Y descriptive system comprises the following 5 dimensions: mobility, looking after myself, doing usual activities, having pain or discomfort and feeling worried, sad or unhappy. Each dimension has 3levels: no problems, some problems and a lot of problems. The EQ VAS records the younger patient’s self-rated health on a vertical VAS where the endpoints are labelled “The best health you can imagine” and “The worst health you can imagine”.

Participants will complete the questionnaire as described in the SoA (Section 1.3). The assessment tool is provided in Section 10.7.9 and Section 10.7.10.

8.1.8 Missed school/work days

Participants who are employed or enrolled in school will be asked to report the number of sick leave/missed school days since the last study assessment.

Participants will complete the questionnaire as described in the SoA (Section 1.3). The assessment tool is provided in Section 10.7.11.

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 adverse event.

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

- Single standard 12-lead ECG will be obtained as outlined in the SoA (see 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.

8.2.4 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests 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 CRF. 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, unless judged by the Investigator to be more severe than expected for the participant's condition.
- 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 or Medical Monitor.
- 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 CRF.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Adverse event of special interest

An adverse event of special interest (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.

For these AESIs, the Sponsor will be informed immediately (ie, within 24 hours), per SAE notification described in Section 10.3, even if not fulfilling a seriousness criterion, using the corresponding pages in the CRF (to be sent) or screens in the e-CRF.

- 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 subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP/non-investigational medicinal product (NIMP)
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills 1 of the seriousness criteria
  - 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.
  - Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

- Symptomatic overdose (serious or nonserious) with IMP/NIMP
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant 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 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 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".

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

Adverse event 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 AE or SAE after conclusion of the 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 AE and SAE 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 AEs of special interest (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 given in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a 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.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- Adverse events that are considered expected will be specified in the reference safety information.
- An Investigator who receives an Investigator safety report describing a SAE or 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.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and 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).
- 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

The CSU 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 Guidelines for reporting product complaints

Any defect in the IMP/NIMP must be reported as soon as possible by the Investigator to the monitoring team that 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.

8.3.8 Patients with angioedema

Patients with CSU can have angioedema as part of their symptoms. Participants will be provided emergency contact information and advised to contact a physician, in case of new occurrence of angioedema or worsening of preexisting angioedema.

8.4 TREATMENT OF OVERDOSE

Symptomatic overdose with IMP/NIMP is considered as an AESI (defined in Section 8.3).
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 Medical Monitor 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 study intervention if requested by the Medical Monitor (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 Medical Monitor based on the clinical evaluation of the participant.

8.5 PHARMACOKINETICS

8.5.1 Systemic drug concentration and anti-drug 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 collection, storage, and shipping of serum are described in separate operational manuals. The date of collection should be recorded in the participant e-CRF.

8.5.1.2 Handling procedures

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

Table 4 - Summary of handling procedures

[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

[redacted]

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. 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 ADA and PK samples may be collected after the EOS visit until resolution of AE.

Specifically for PK, any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.6 PHARMACODYNAMICS

See Section 8.8 for IgE measurement. No other pharmacodynamic 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. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study. Adolescents/children will not participate in the optional genetic research.

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 a laboratory manual.

8.8 BIOMARKERS

- Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA (Section 1.3):
  - Venous blood samples will be collected for measurement of serum total IgE, which will be measured 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 (except pediatric participants)
    - Serum and plasma will be collected and stored for analysis of potential biomarkers of drug response, disease activity, safety, and the Type 2 inflammation pathway.
  - Skin biopsy (sub-study) (except pediatric participants)
    - For skin biopsies, gene expression and immunohistological analyses may be used to investigate drug response, disease activity, and the Type 2 inflammatory pathway. Two biopsies will be taken from each participant, 1 from lesion and 1 from non-lesion at the timepoints specified in the SoA.
  - Basophil activation test (sub-study) (except pediatric participants in Study A and Study B, and all Study C participants)
    - Blood will be collected for assessment of basophil activation using a validated assay.

Plasma, serum, and skin biopsy samples may be stored for a maximum of 5 years and DNA or RNA samples for 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor.

8.9 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Number of missed school/work days collection is described in Section 8.1.8.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

In Studies A (omalizumab naïve), B (omalizumab intolerant or incomplete responders), and C (omalizumab naïve) the statistical hypotheses for comparing dupilumab against placebo on the primary endpoint of change from baseline in ISS7 at Week 24 (except EU and EU reference countries), and the primary endpoint of change from baseline in UAS7 at Week 24 for EU and EU reference countries are as follows:

- 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 secondary endpoints can be specified similarly as those on the primary endpoint.

9.2 SAMPLE SIZE DETERMINATION

The total anticipated number of participants across the 3 studies is approximately 384 randomized participants.

For Study A (omalizumab naïve): An effect size of 0.7 or higher is assumed. An absolute change of 5 in ISS7 score is considered the minimal clinically important difference (MCID) and an absolute change of 10 in UAS7 score is considered the MCID. Based upon an SD of 7, a change of 5 in the ISS7 would correspond to an effect size of approximately 0.7. Based upon an SD of 14, a change of 10 in the UAS7 would correspond to an effect size of approximately 0.7. Based on this assumption, plus the assumption of a 15% dropout rate and inclusion of children, it is estimated that 65 participants per group will provide 96% power to detect an effect size of 0.7 or higher between the dupilumab arm and placebo using a 2-sided t-test with alpha = 0.05. This sample size estimate applies to both ISS7 (primary endpoint for all countries except EU and EU reference countries) and UAS7 (primary endpoint for EU and EU reference countries).

For Study B (omalizumab intolerant or incomplete responders): An effect size of 0.7 or higher is assumed. An absolute change of 5 in ISS7 score is considered the MCID and an absolute change of 10 in UAS7 score is considered the MCID. Based upon an SD of 7, a change of 5 in the ISS7 would correspond to an effect size of approximately 0.7. Based upon an SD of 14, a change of 10 in the UAS7 would correspond to an effect size of approximately 0.7. Based on this assumption, plus the assumption of a 15% dropout rate, it is estimated that 52 participants per group, will provide 90% power to detect an effect size of 0.7 or higher between the dupilumab arm and placebo using a 2-sided t-test with alpha = 0.05. This sample size estimate applies to both ISS7 (primary endpoint for all countries except EU and EU reference countries) and UAS7 (primary endpoint for EU and EU reference countries).

Considering the reduced drop-out rate of 10% observed during the study, an interim analysis will be performed when the first 80 randomized participants would have completed their Week 24 visit by the interim analysis cut-off date. Using the O'Brien-Fleming approach with information fraction 0.77 and overall type-I error controlled at 0.05, the alpha spending at this interim analysis will be 0.021, and the alpha spending at the final analyses when all 104 participants complete the study will be 0.043.

At the Study B interim analysis, it is estimated that 40 participants per group will provide 74% power to detect a treatment effect of 5 or higher with SD 7 and minimal detectable difference (MDD) of approximately 3.8 for ISS7 and a treatment effect of 10 or higher with SD 14 and MDD of approximately 7.6 for UAS7 between the dupilumab arm and placebo using a 2-sided t-test with alpha = 0.021.

With the decision process outlined in Section 9.5, the overall power for the study will be approximately 88%.

For Study C (omalizumab naïve): Assumptions for sample size calculations for Study C were made by considering Study A results. An effect size of 0.564 or higher is assumed. Based upon an SD of 7.5 (pooled SD from the observed data in Study A), a treatment difference of 4.23 in the ISS7 would correspond to an effect size of approximately 0.564. Based upon an SD of 14.3 (pooled SD from the observed data in Study A), a treatment difference of 8.53 in the UAS7 would correspond to an effect size of approximately 0.597. Based on this assumption, plus the assumption of a 10% dropout rate, it is estimated that 75 participants per group will provide 90% power to detect an effect size of 0.564 or higher between the dupilumab arm and placebo using a 2-sided t-test with alpha = 0.05. This sample size estimate applies to both ISS7 (primary endpoint for all countries except EU and EU reference countries) and UAS7 (primary endpoint for EU and EU reference countries).

The sample size calculations and the alpha spending by O'Brien-Fleming approach were calculated by nQuery Advisor and nTerim 4.0.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis which will be conducted separately for each study (A, B and C), the following populations are defined separately for each study (A, B and C) (Table 6):

Table 6 - Populations for analyses

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.

Population	Description
Intent-to-treat24 (ITT24) (For Study B interim analysis)	All participants who were randomized at least 24 weeks before the interim analysis cut-off date and would have completed the Week 24 visit by the cut-off date of interim analysis. The exact interim analysis cut-off date will be specified in the SAP, which will be finalized before the interim analysis.
Efficacy	The ITT population (ITT24 for Study B interim analysis).
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received. Randomized participants for whom it is unclear whether they took the study medication will be included in the safety population as randomized. For participants who accidentally receive different treatment from the planned, the actual intervention allocation for as-treated analysis will be the dupilumab group. The pharmacodynamic (PD) analyses will be performed on the safety population.
Pharmacokinetic (PK)	The PK population includes all participants in the safety population with at least one non-missing result for functional dupilumab concentration in serum after first dose of the study treatment. 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 one non-missing ADA result after first dose of the study treatment. Participants will be analyzed according to the intervention actually received.

Abbreviations: ADA = antidrug antibody; ICF = Informed consent form, IRT = Interactive response technology; PD = Pharmacodynamic

9.4 STATISTICAL ANALYSES

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1 Efficacy analyses

Table 7 - Efficacy analyses

Endpoint	Statistical analysis methods
Primary Primary endpoint: Change from baseline in ISS7 at Week 24 (except EU and EU reference countries) Primary endpoint for EU and EU reference countries: Change from baseline in UAS7 at Week 24	The primary efficacy endpoint will be analyzed using a hybrid method of the worst-observation carried forward (WOCF) and multiple imputation. For participants taking selected prohibited medications and/or rescue medications (details of selection will be specified in the statistical analysis plan), their data after the medication usage will be set to missing, and the worst postbaseline value on or before the time of the medication usage will be used to impute missing Week 24 value (for participants whose postbaseline values are all missing, the baseline will be used to impute). Participants who discontinue the treatment prematurely are encouraged to follow the planned clinical visits and in these participants who did not take the selected prohibited medications and/or rescue medications, all data collected after treatment discontinuation will be used in the analysis. For these

Endpoint	Statistical analysis methods
	participants, missing data may still happen despite all efforts have been tried to collect the data after treatment discontinuation. For participants who discontinue 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 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 selected prohibited medications and/or rescue medications on or before Week 24 and excluding participants 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 primary endpoint, treatment group, presence of angioedema at baseline, and region (combined countries) as covariates. Statistical inference obtained from all imputed data will be combined using Rubin's rule. Descriptive statistics including number of subjects, 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% confidence intervals (CI) will be provided along with the p-values. 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 UAS7 at Week 12 and Week 24 (except EU and EU reference countries) Change from baseline in HSS7 at Week 12 and Week 24 Change from baseline in ISS7 at Week 12 and Week 24 (in EU and EU reference countries) Change from baseline in AAS7 at Week 12 and Week 24 Change from baseline in UCT at Week 12 and Week 24 Change from baseline in DLQI /CDLQI at Week 12 and Week 24 PGIC at Week 12 and Week 24 Change from baseline in PGIS at Week 12 and Week 24 Change from baseline in ISS at all time points	These endpoints will be analyzed using the same approach as for the primary endpoint of change from baseline in ISS7 at Week 24. Detailed analyses will be described in the SAP finalized before database lock.
Secondary Proportion of ISS7 MID responders at Week 12 and Week 24 Proportion of patients with UAS7 $\leq$6 at Week 12 and Week 24 Proportion of patients with UAS7 = 0 at Week 12 and Week 24	These responder endpoints will be analyzed using the Cochran-Mantel-Haenszel test adjusted by baseline disease severity, presence of angioedema at baseline, and region. The baseline disease severity will be defined according to UAS7 <28 or ≥28. Comparisons of the response rates between dupilumab dose and placebo will be derived.

Endpoint	Statistical analysis methods
Proportion of well-controlled patients (UCT ≥12) at Week 12 and Week 24	Participants who receive selected prohibited medications and/or rescue medications will be considered as non-responders 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 responder/non-responder status. Missing data will be considered as non-responders.
Secondary Time to ISS7 MID response Proportion and time to event of patients receiving OCS for CSU during the planned treatment period	These time-to-event endpoints will be analyzed using the Cox proportional hazards model, including treatment, the corresponding baseline value, presence of angioedema at baseline, and region as covariates. The estimates of the hazard ratio between dupilumab dose and placebo will be derived.
Exploratory	Will be described in the SAP finalized before database lock.

Within each study, Study A and Study C (omalizumab naïve) and Study B (omalizumab intolerant or incomplete responders), the multiplicity procedure is proposed to control the overall Type-I error rate for testing the primary endpoint and the key secondary endpoints. Detailed hierarchical testing procedure will be defined in each study SAP.

Study A and Study C are each considered positive when the primary endpoint achieves statistical significance with 2-sided significance level 0.05 for that study.

For study B, an interim analysis will be performed using the O'Brien-Fleming approach with information fraction 0.77 and overall type-I error controlled at 0.05, the alpha spending at this interim analysis will be 0.021, and the alpha spending at the final analyses when all 104 participants complete the study will be 0.043. The decision process that applies to this interim analysis is outlined in Section 9.5.

Multiplicity adjustment for the other efficacy endpoints will be described in the study SAP.

9.4.2 Safety analyses

All safety analyses will be performed on the safety population. 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 study intervention. Serious AEs and AEs leading to study discontinuation that occur outside the treatment-emergent period will be summarized separately.

Endpoint	Statistical Analysis Methods
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 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 by 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 post baseline time point, endpoint, 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. The proportion of participants who had at least one 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.

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 clinical study report (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 required to investigate the impact of COVID-19 or other pandemics pandemic requiring public health emergency on the efficacy (eg, missing data due to COVID-19) and safety will be detailed in the SAP.

9.5 INTERIM ANALYSES

The database locks will be implemented separately for Study A (omalizumab naïve), Study B (omalizumab intolerant or incomplete responders), and Study C (omalizumab naïve).

No interim analysis is planned for Study A and Study C.

For each Study A and Study C, 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.

For Study B, an interim analysis (IA) will be performed when the first 80 randomized participants would have completed their 24-week treatment period by the interim analysis cut-off date. This interim analysis will use the O'Brien-Fleming approach with information fraction 0.77 and overall type-I error controlled at 0.05, with an alpha spending at the interim analysis of 0.021, and an alpha spending at the final analysis (when all 104 participants complete the study) of 0.043.

The possible outcomes from this interim analysis are summarized below and in Table 9:

Efficacy at IA:

- In case p-value at interim analysis is ≤0.021 in ISS7 and UAS7, Study B is considered "Efficacy at IA for ISS7 and UAS7" (as shown in Table 9).
- In case p-value at interim analysis is ≤0.021 for ISS7 and >0.1 for UAS7, Study B is considered "Efficacy at IA for ISS7" (as shown in Table 9).

In case of "Efficacy at IA", the cut-off date for the interim analysis will be considered as the primary database lock, the study treatment will continue, and a final database lock will occur when all participants have completed the last visit in the study. Additional data between this database lock and last participant completing last visit will be summarized in a CSR addendum.

Stop for futility:

- In case p-value at interim analysis is >0.1 for ISS7 and UAS7, Study B is considered "Stop for futility" (as shown in Table 9).

In case of stop for futility, enrollment of additional patients will stop for Study B if 104 patients have not been enrolled and the study treatment will be stopped for all current participants. Additional data between this database lock and last participant completing last visit will be summarized in a CSR addendum.

Continue up to EOT for the primary analysis:

- For all other situations the decision is to continue the study (as shown in Table 9) until 104 participants (52 participants per group) complete the study treatment and the final analysis will be conducted with an alpha 0.043.

In this case Study B will continue up to the EOT for the primary analysis, a second database lock will be performed when all randomized participants have completed their treatment phase and a final database lock will occur when all participants have completed the last visit in the study.

Table 9 - Possible outcomes from the Study B interim analysis

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

To maintain study integrity with respect to the subsequent visits and analyses after the Study B interim analysis, a dissemination plan will be written. This plan will clearly identify two independent study teams and an independent committee (including a statistician). Details of the process will be described in the Study SAP.

The independent committee will be in charge of analyzing and reviewing the interim analysis and providing guidance about the above described scenarios (continue, success or futility).

Two independent study teams will be put in place. Specific steps will be setup to maintain the blind of the study to all individuals involved in the conduct of the study and/or analysis, and to protect the overall blinding and integrity of the study data, after the interim analysis has been performed. Details will be provided in the dissemination plan.

9.5.1 Data Monitoring Committee

Due to extensive safety record of the post-marketed IMP (dupilumab), it is not planned to have a Data Monitoring Committee for this study.

9.5.2 Unblinding plan

The unblinding plan will be detailed in the SAP or in a separate unblinding plan.

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.
- 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 site and adherence to requirements of 21 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/child) or his/her legally authorized representative and answer all questions regarding the study. All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.
- It is the responsibility of the Investigator or designee (if acceptable by local regulations) to obtain written informed assent form (IAF) from each participant ≥6 years of age, and written ICF from each participant's parent(s)/caregiver(s)/legally authorized representative(s), prior to the participant's participation in the study, and prior to initiating any screening procedures. The written IAF/ICF should be signed and dated by the participant(s) and parent(s)/caregiver(s)/legally authorized representative(s), respectively.
- Participants must be informed that their participation is voluntary. Participants (and parents of adolescents/children) 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 and children will sign simplified informed consent (IAF). If during the study the adolescent reaches the age of majority he/she needs to re-consent.
- The ICF and possibly the IAF used by the Investigator for obtaining the informed consent of the participant and parent(s) or the participant's legally acceptable representative must be reviewed and approved by the Sponsor prior to submission to the appropriate IRB/IEC for approval/favorable opinion.
- For the children/adolescents' participation, local law must be observed in deciding whether one or both parents/ legally authorized representatives' consent is required. If only one parent or legally authorized representative signs the consent form, the Investigator must document the reason for only one parent or legally authorized representative's signature.
- In addition, children/adolescents will assent as detailed below or will follow the Ethics Committee (IRB/IEC) approved standard practice for pediatric participants at each participating center (age of assent to be determined by the IRBs/IECs or be consistent with the local requirements):
  - Participants who can read the IAF will do so before writing their name and dating or signing and dating the form.
  - Participants who can write but cannot read will have the IAF read to them before writing their name on the form.
- The original of each completed IAF/ICF must be retained by the Investigator as part of the participant's study record and a copy of the signed assent/consent form must be given to the participant(s)/participant's parent(s)/caregiver(s)/legally authorized representative(s).
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled 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.

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

For adults only, adults will have the option to provide consent for the use of remaining mandatory samples as well as any remaining additional serum/plasma samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory 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.

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 (Global Data Protection Regulation).

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)".

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- 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.
- 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.
- 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.

10.1.5 Committees structure

There will be no study committees.

10.1.6 Dissemination of clinical study data

Sanofi shares information about clinical trials and results on publically 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 clinical trial register (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials 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 clinicalstudydatarequest.com.

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

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.
- 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 site 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.
- Definition of what constitutes source data can be found in Study Reference Manual.

10.1.9 Study and site closure

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

The Investigator may initiate study-site 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 site 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 site 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 site 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 10 will be performed by the central laboratory.

- 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 10 - 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 [fasting or nonfasting]
	Potassium
	Lactate dehydrogenase
	Uric acid
	Total cholesterol
	Sodium
	Calcium
	Chloride
	Bicarbonate
	Creatine Phosphokinase
	Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic transaminase (SGOT)
	Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase (SGPT)
	Alkaline phosphatase
	Total bilirubin
	Total protein
	Albumin

Laboratory assessments	Parameters
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, and ketones [bilirubin, urobilinogen, nitrite, and leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal)
Other screening tests	• For women of childbearing potential[b]: serum pregnancy test at screening visit (Visit 1) and urine pregnancy tests every 4 weeks during the study. A negative result must be obtained at V1 and at V2 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 site visits planned. 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. • HIV serologic testing at screening visit (Visit 1): Human Immunodeficiency Virus (HIV) screen (Anti-HIV-1 and HIV-2 antibodies)

NOTES:

a Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 10.6. All events of [insert criteria related to ALT, bilirubin, International normalized ratio etc] which may indicate severe liver injury (possible Hy's Law) must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

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

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.

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 one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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 CRF.
- 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 such case, care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the study are properly mentioned on any copy of a source document provided to the Company.
- 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 one 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.

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 site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site 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 site 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 post-menopausal 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 site personnel's: 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 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.

Highly effective contraceptive methods that are user dependent[a] *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
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly effective methods that are user independent[a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion
Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
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.*

NOTES:

a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

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 dupilumab.
- 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

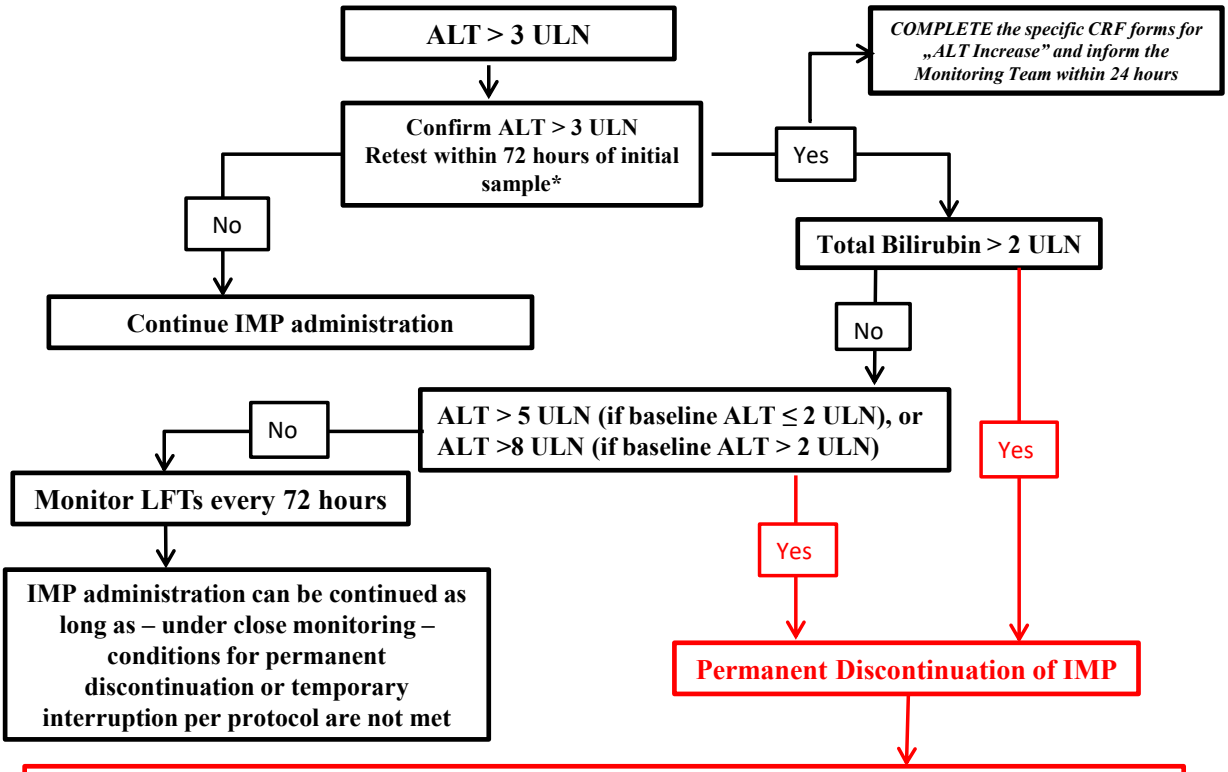
- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed 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 will be reported as an AE or SAE. A spontaneous abortion 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 of the protocol. 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 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, a blood sample will be collected for DNA analysis from consenting participants.
- DNA and RNA samples will be used for research related to dupilumab or chronic spontaneous urticaria 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: SUGGESTED 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:**
   - A*s 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 laboratory results to decide on further reporting/monitoring/discontinuation.

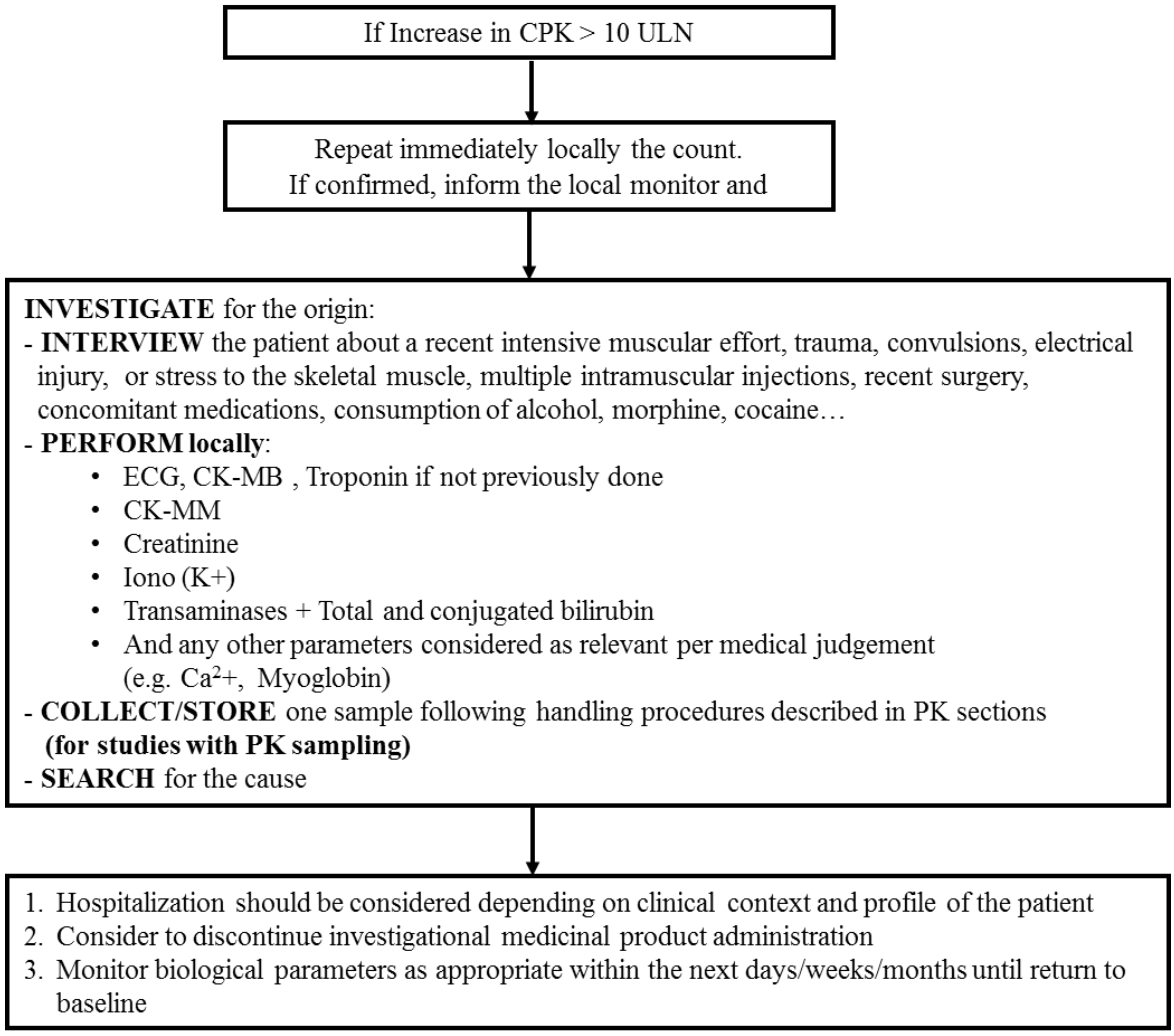
Note:

"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.

INCREASE IN CPK OF NON-CARDIAC ORIGIN AND NOT RELATED TO INTENSIVE PHYSICAL ACTIVITY



Increase in CPK is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting adverse events in Section 10.3 is met.

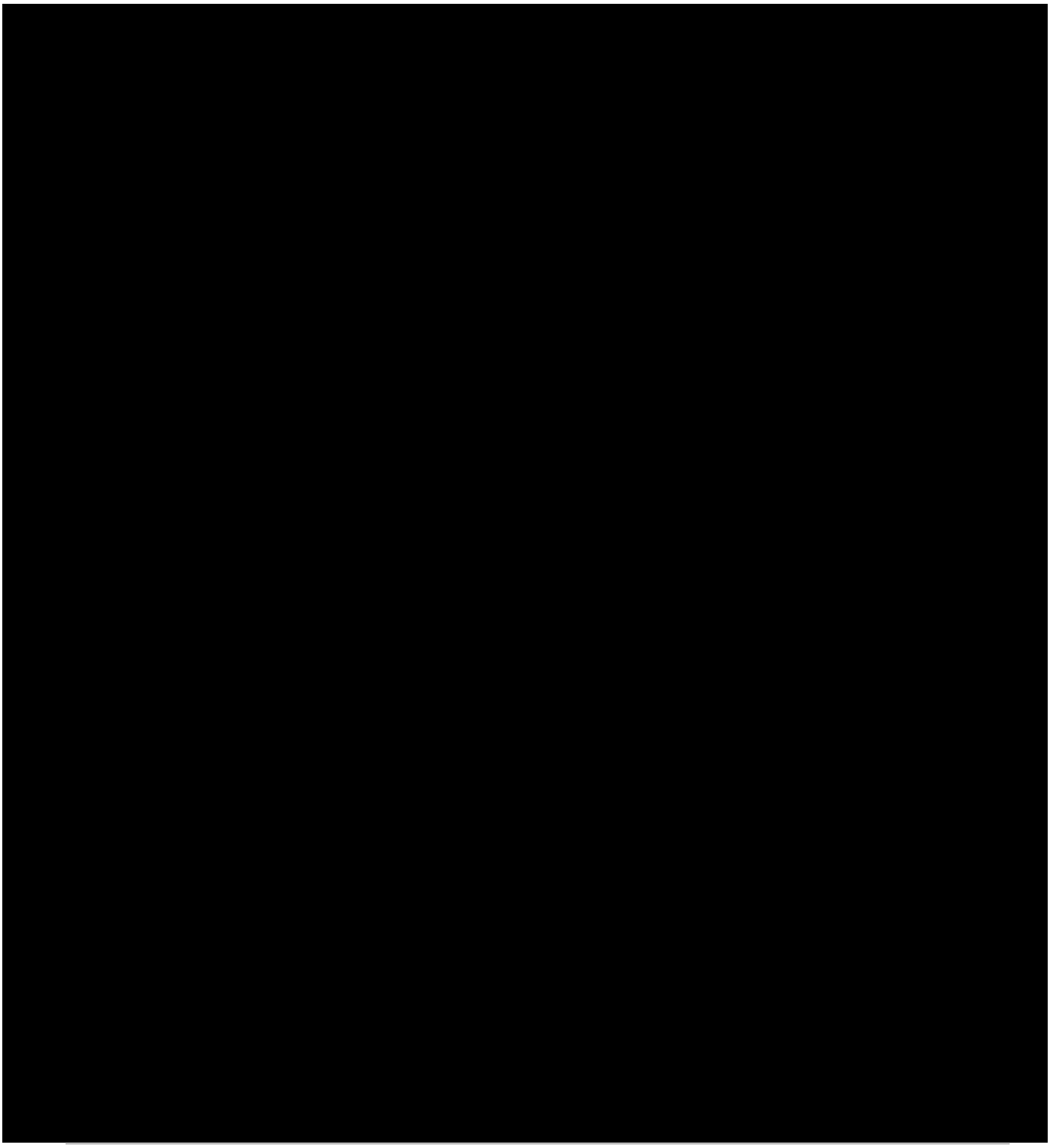
10.7 APPENDIX 7: CLINICIAN-REPORTED OUTCOMES AND PATIENT-REPORTED OUTCOMES

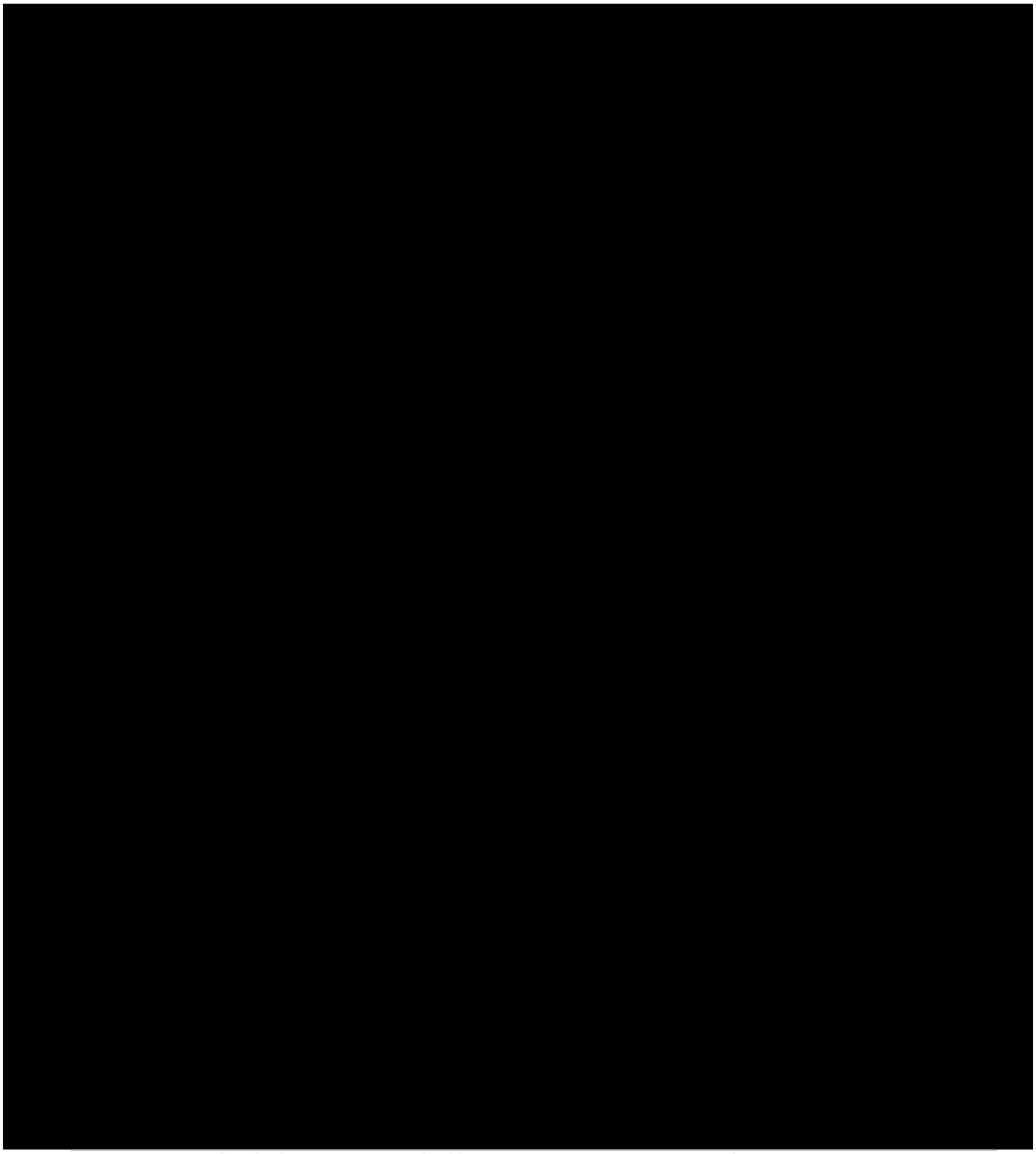
10.7.1 Urticaria activity score (UAS)

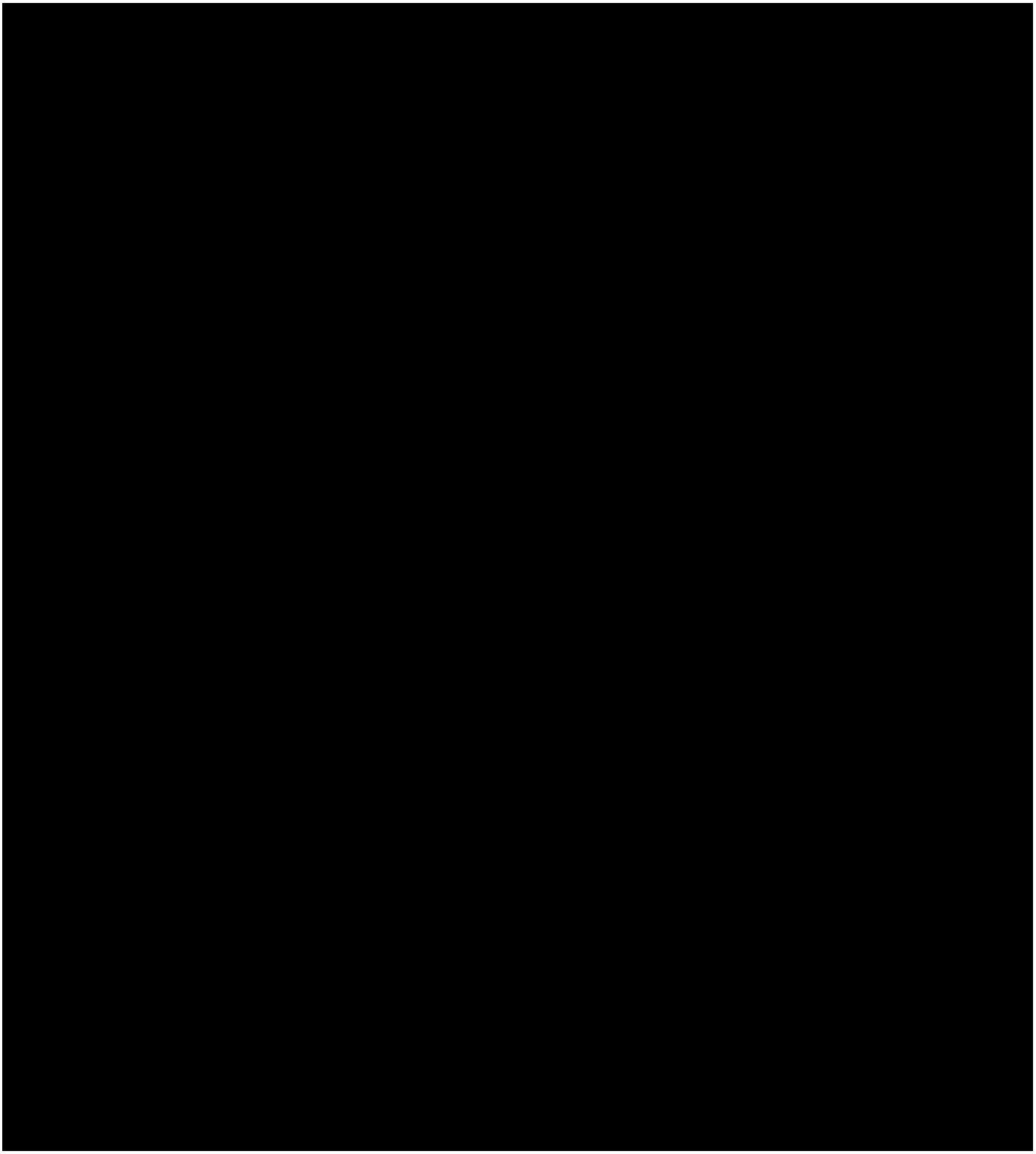
Copyrights:

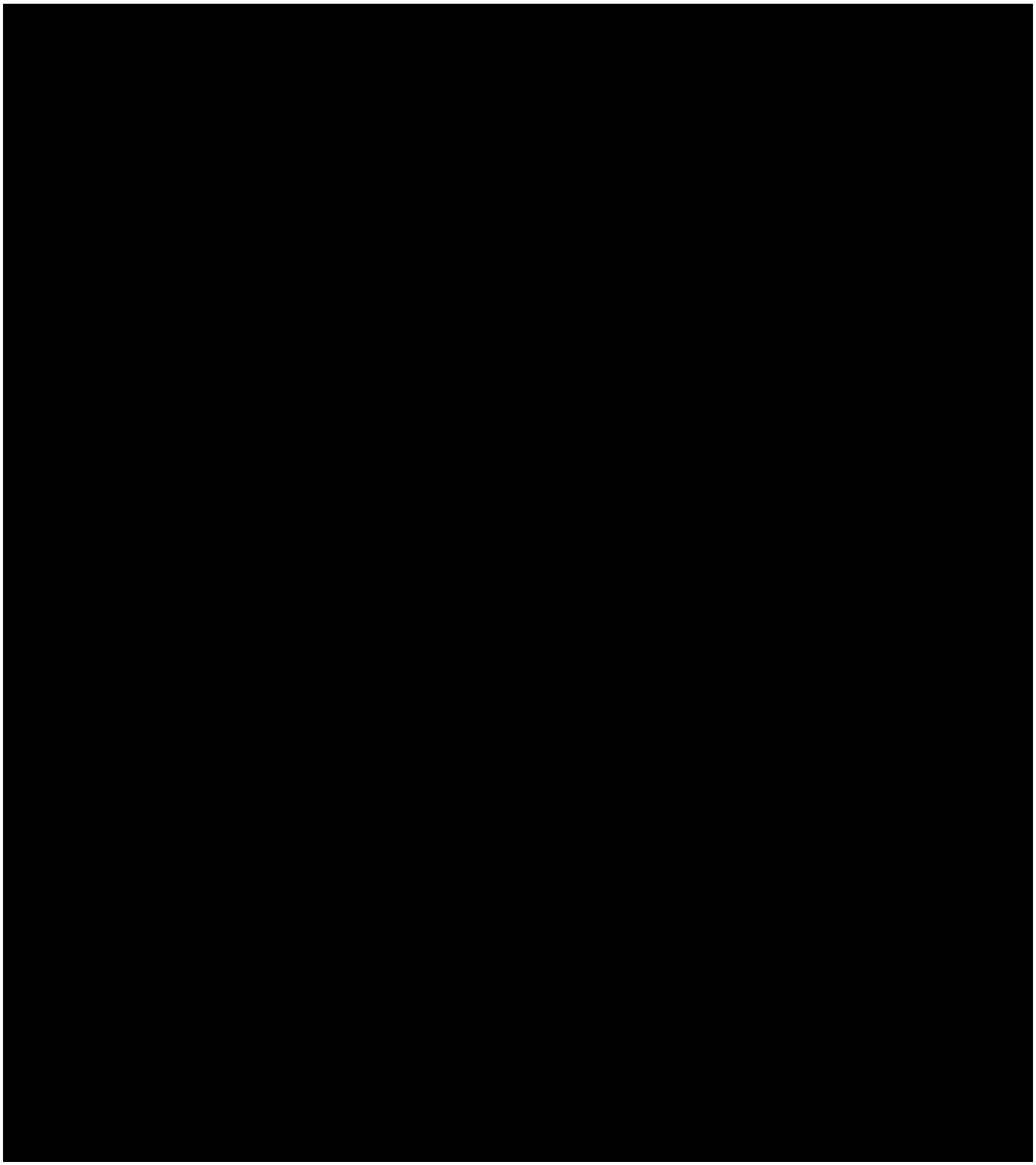
1. Zuberbier T, et al., Pseudoallergen-free diet in the treatment of chronic urticaria. A prospective study. Acta Derm Venereol. 1995 Nov; 75(6):484-7
2. Zuberbier T, et al., The EAACI/GA²LEN/EDF/AAAAI/WAO/ Guideline for the definition, classification, diagnosis and management of Urticaria - The 2013 revision and update. Allergy. 2014; 69(7):868-887.
3. The address of the GA²LEN website: www.ga2len.net

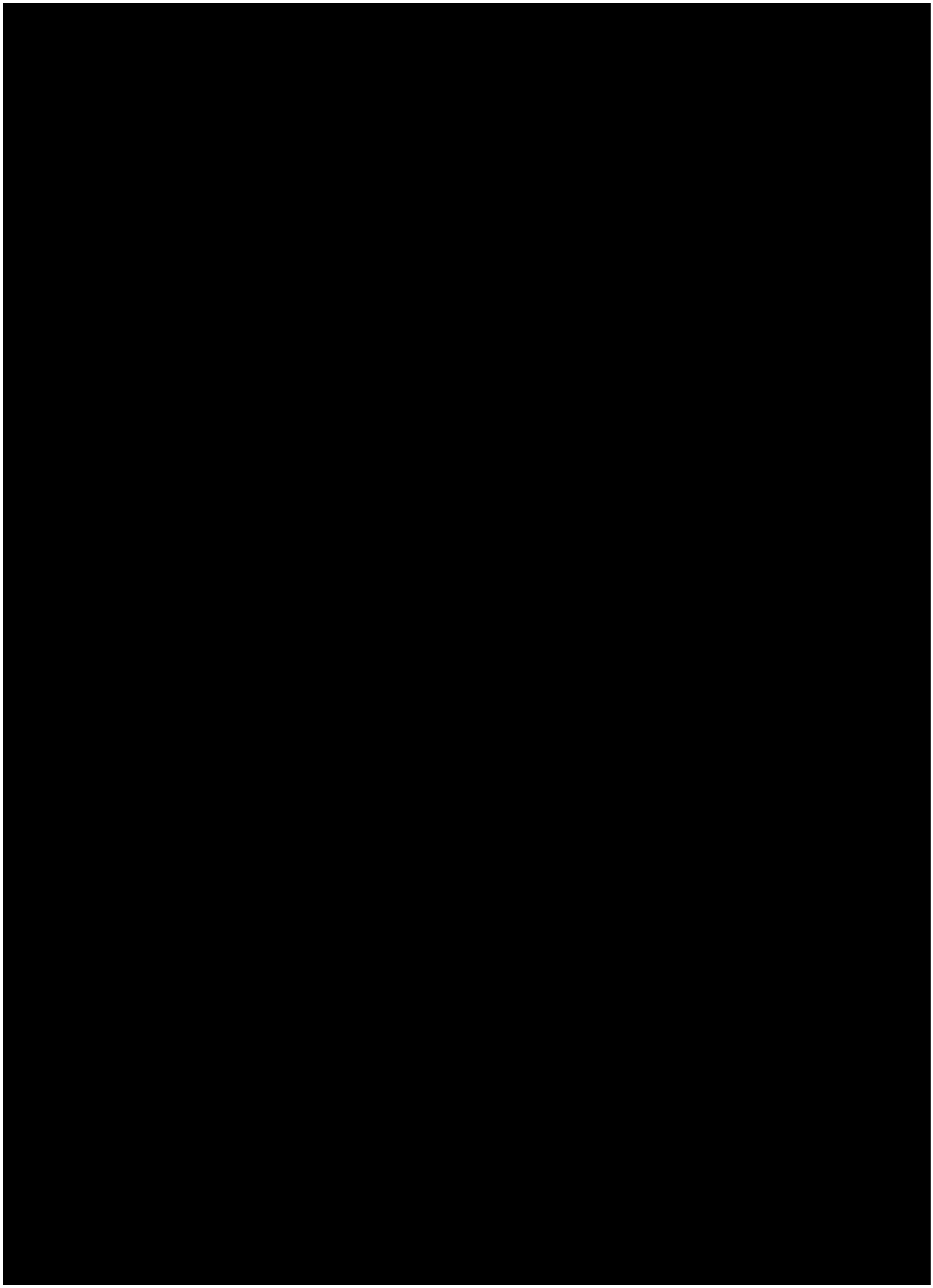
10.7.2 Angioedema activity score (AAS)

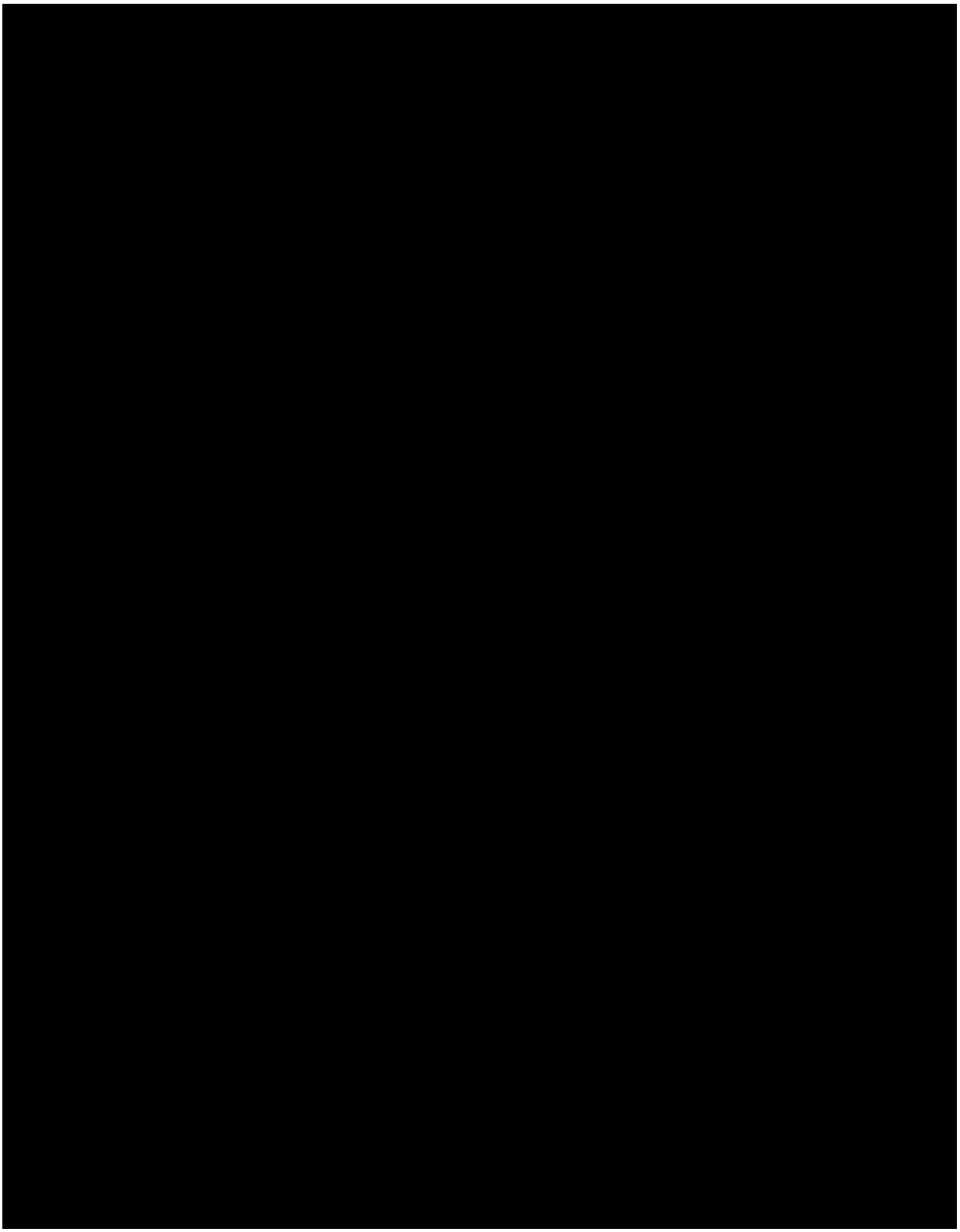






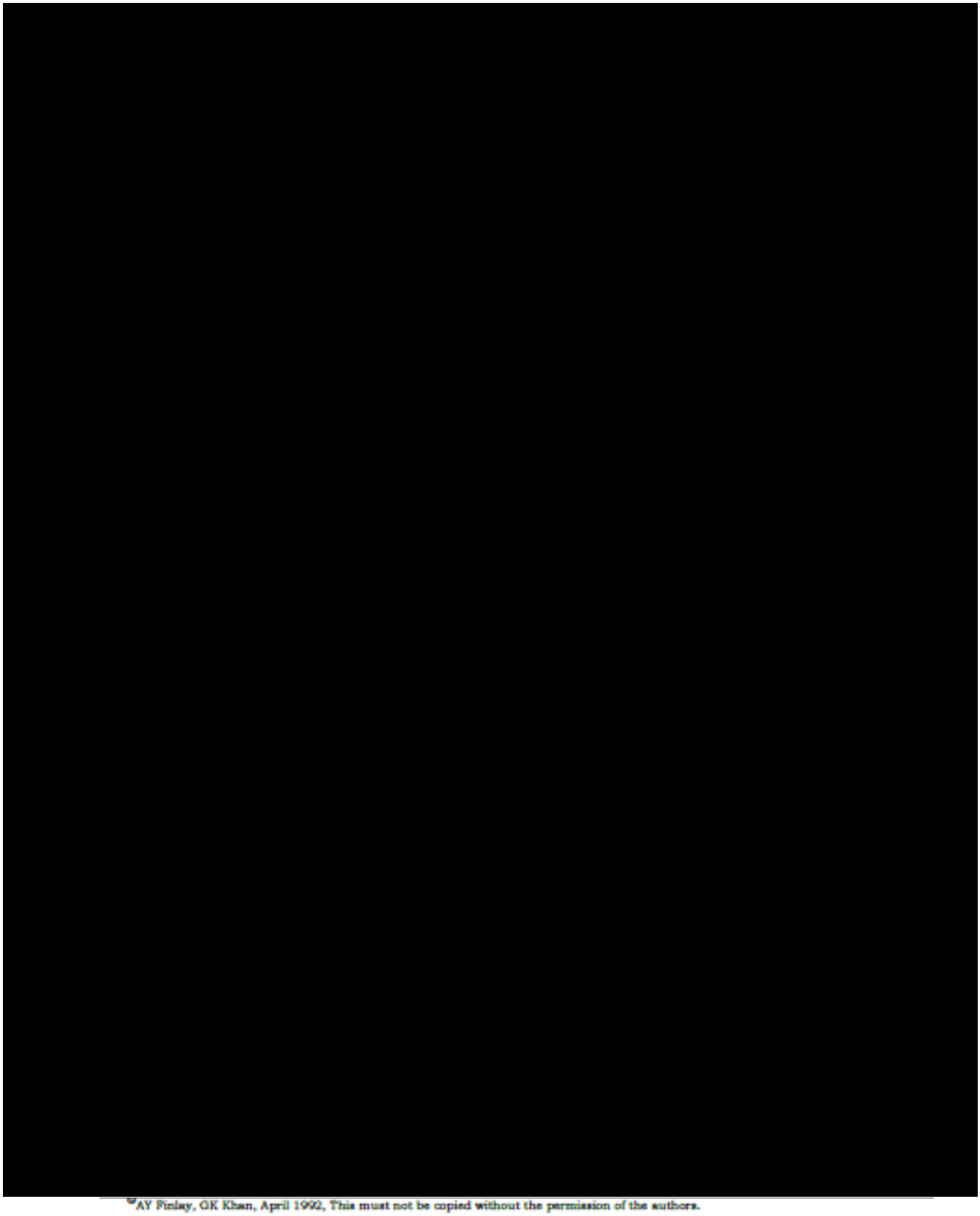




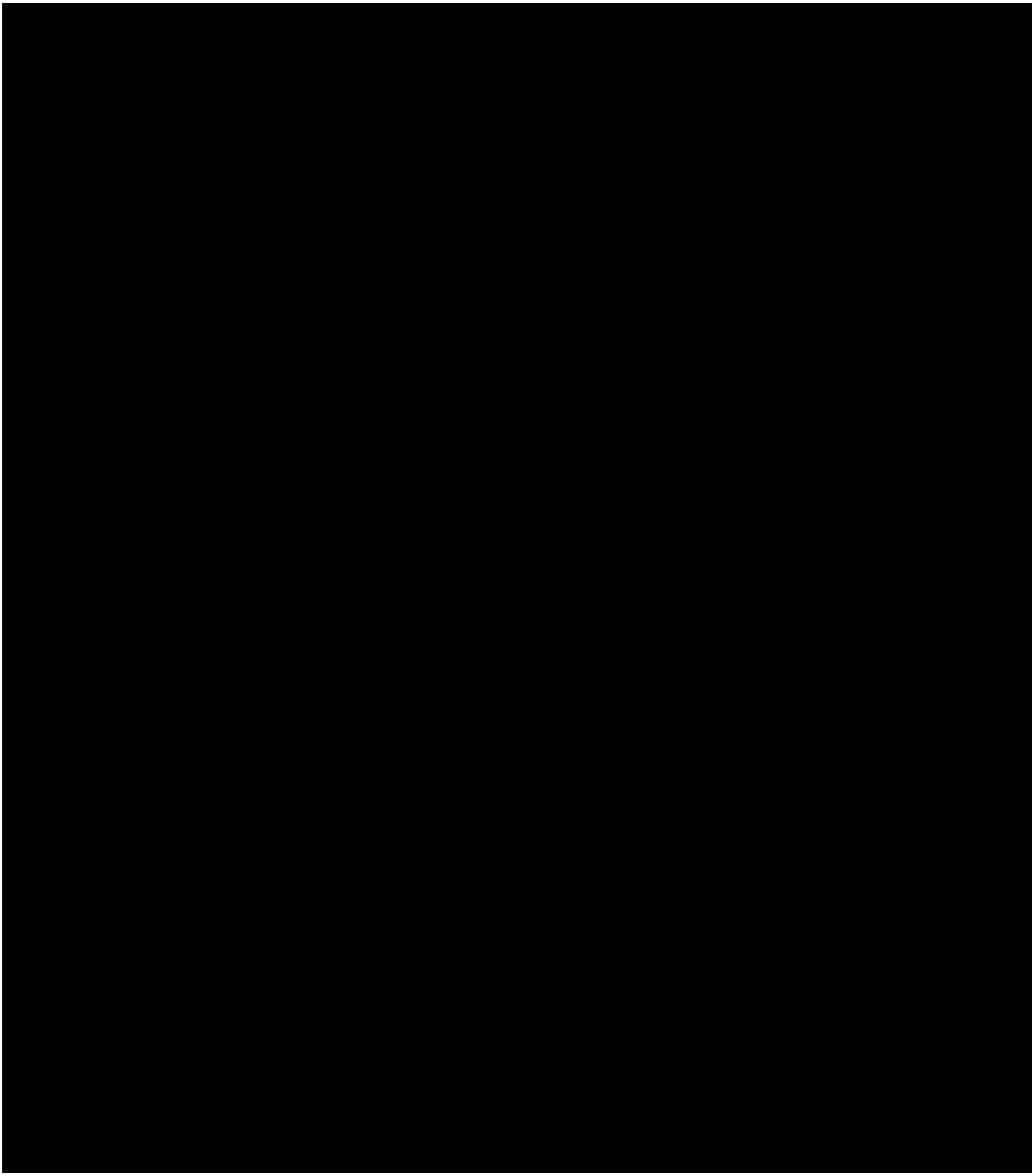


10.7.3 Urticaria control test (UCT)

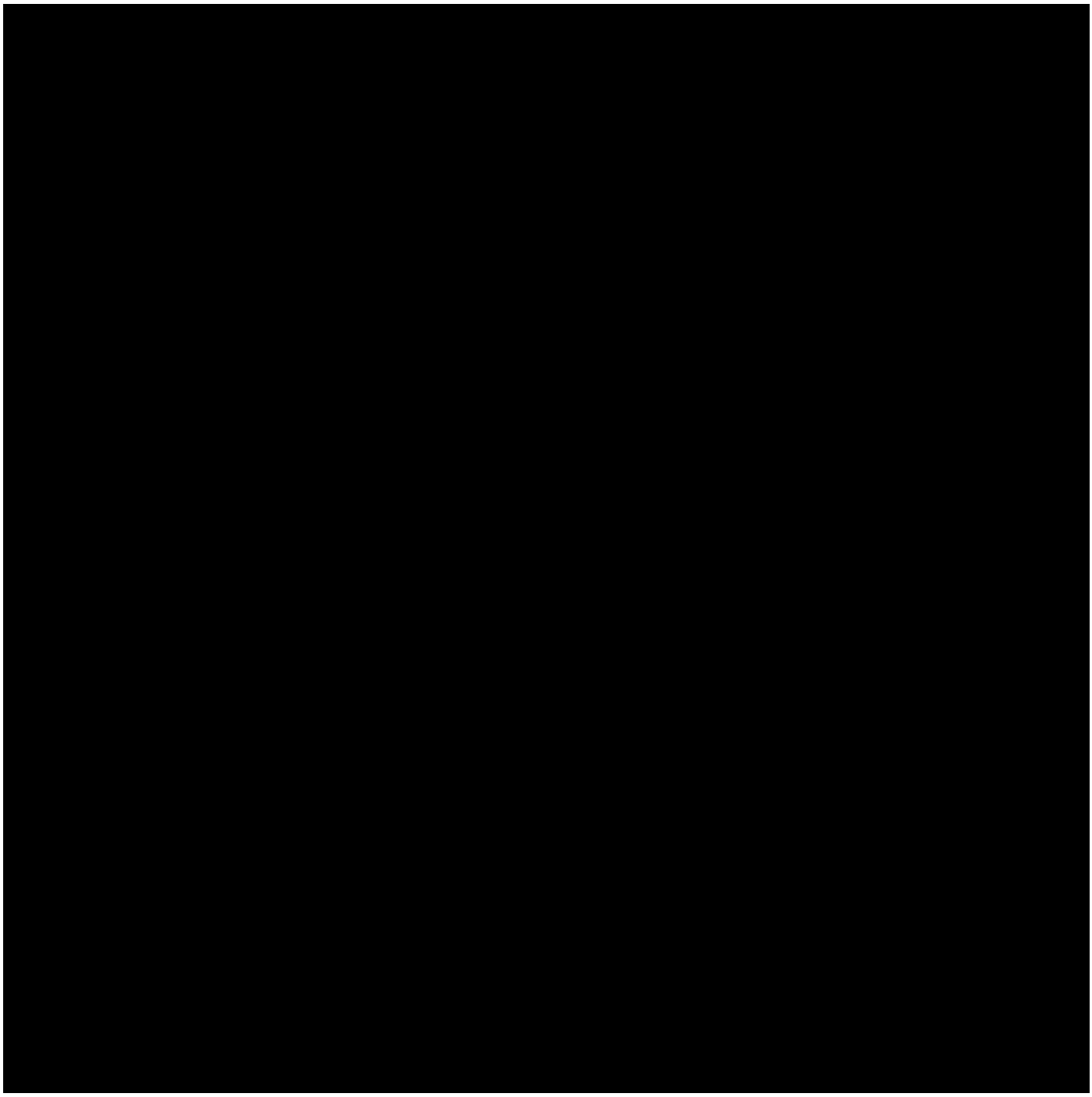
10.7.4 Dermatology life quality index (DLQI)

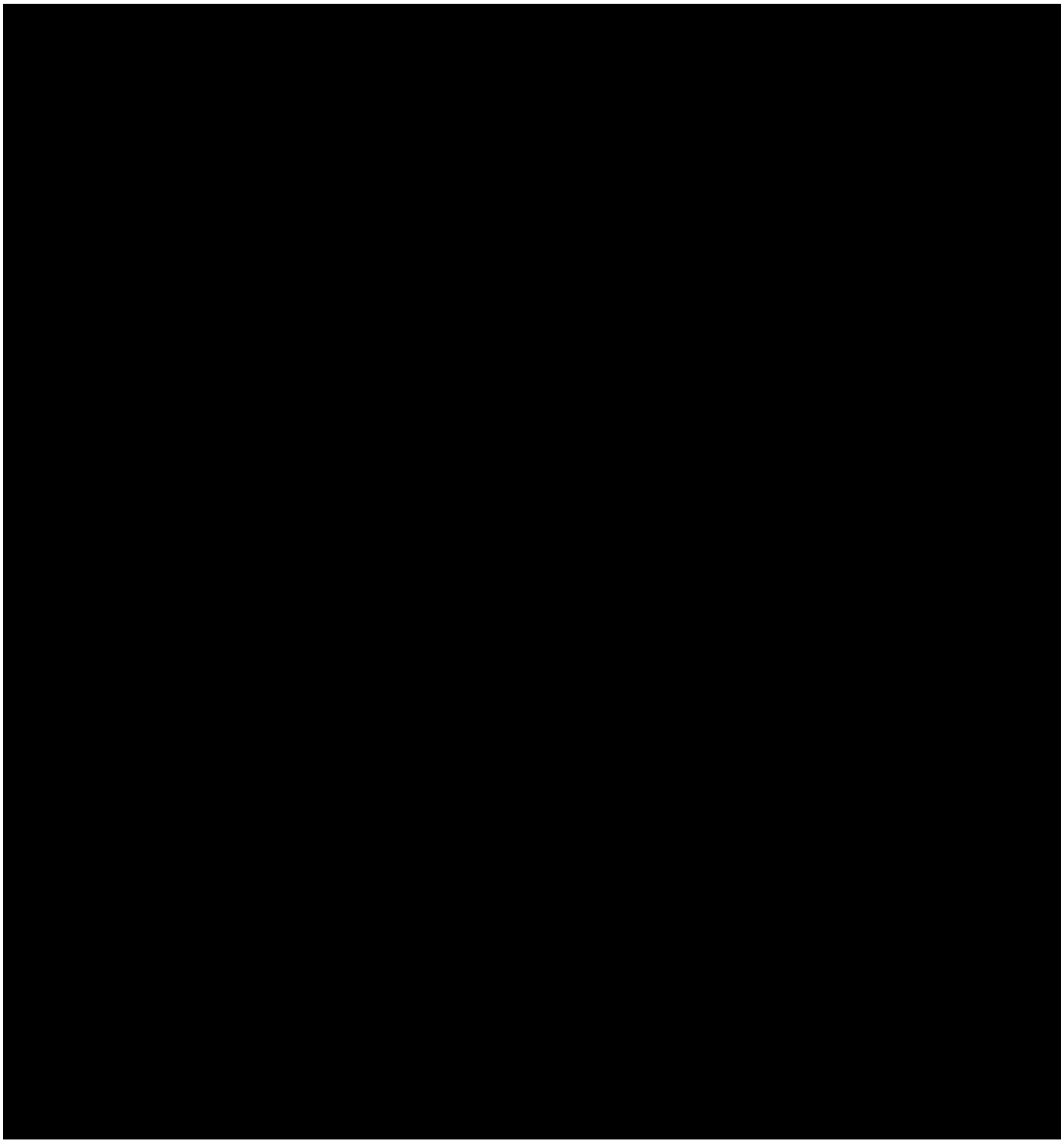


10.7.5 Children's dermatology life quality index (CDLQI)



10.7.6 Chronic urticaria quality of life questionnaire (CU-Q2OL)





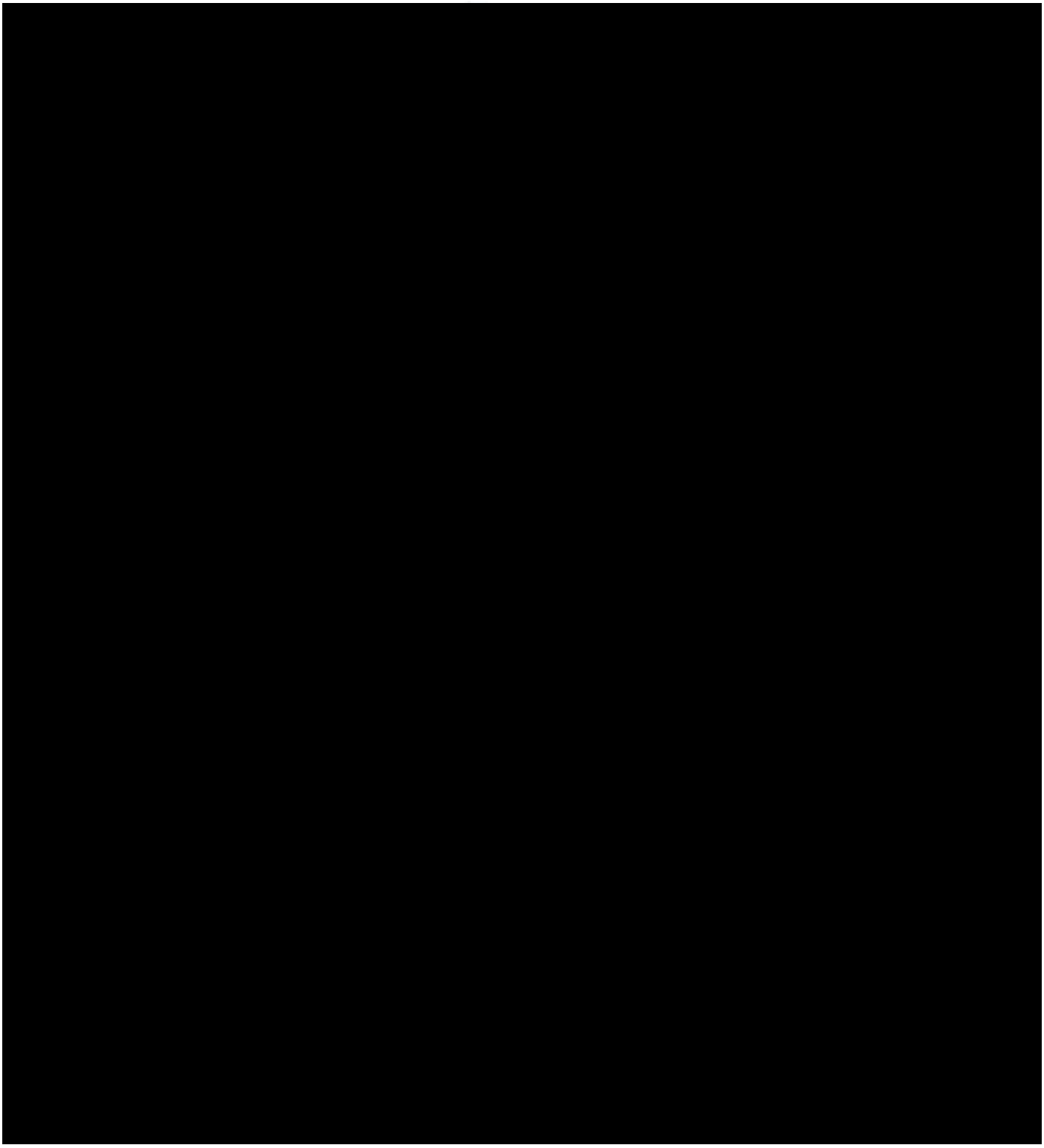
10.7.7 Patient Global Impression of Change (PGIC)

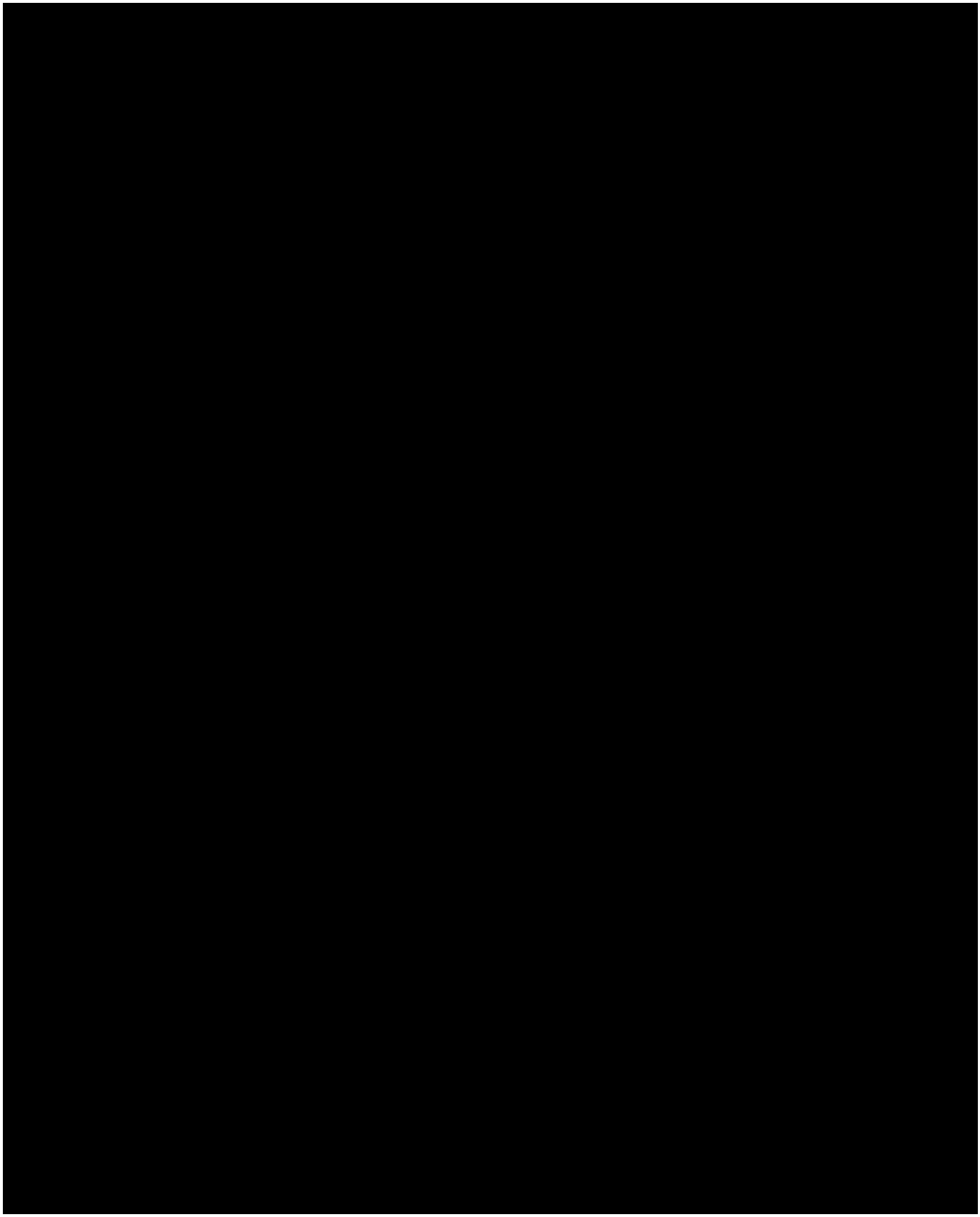
[redacted]

10.7.8 Patient Global Impression of Severity (PGIS)

[redacted]

10.7.9 EuroQol 5-dimensional questionnaire Youth (EQ-5D-Y)

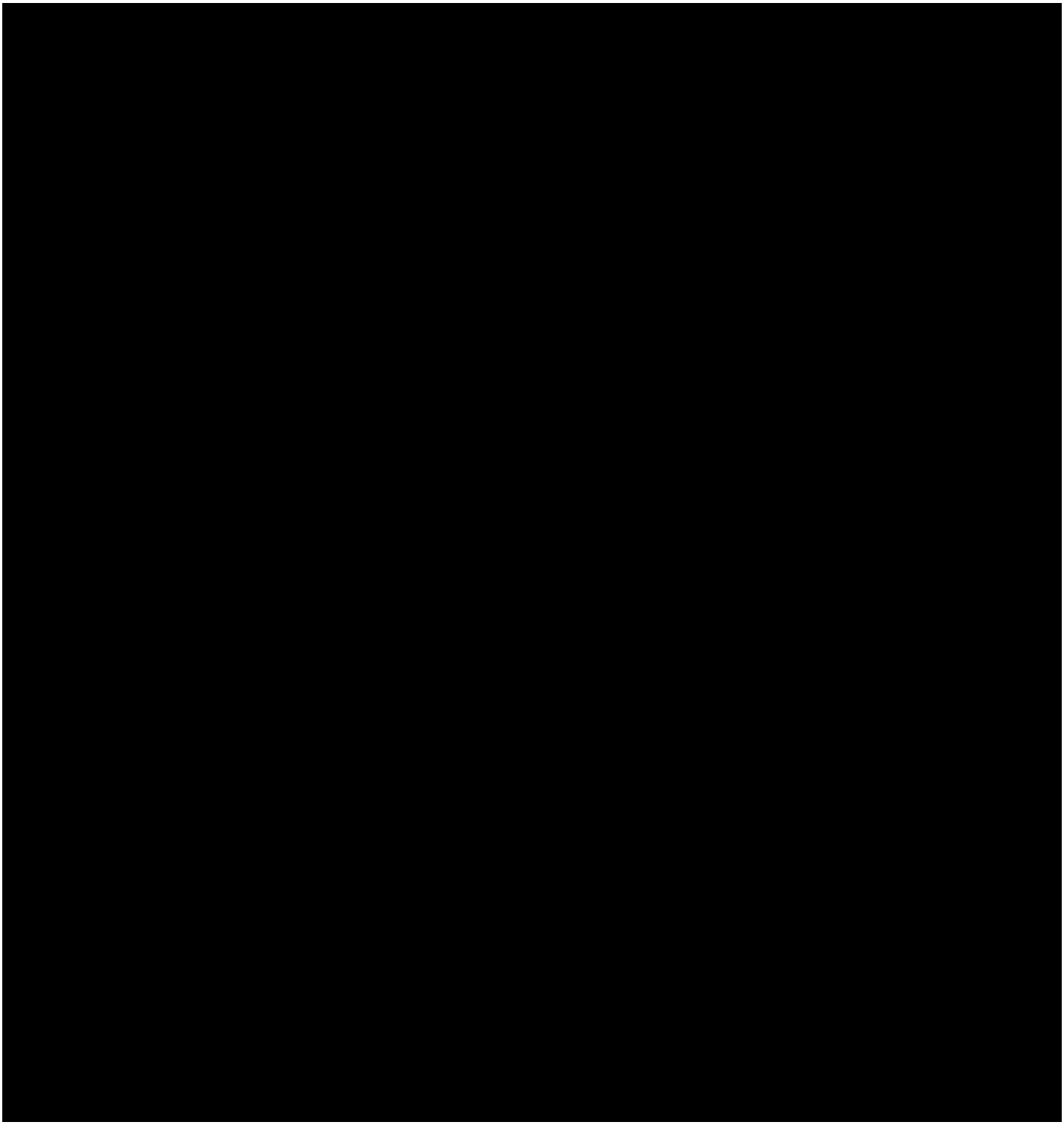




[redacted]

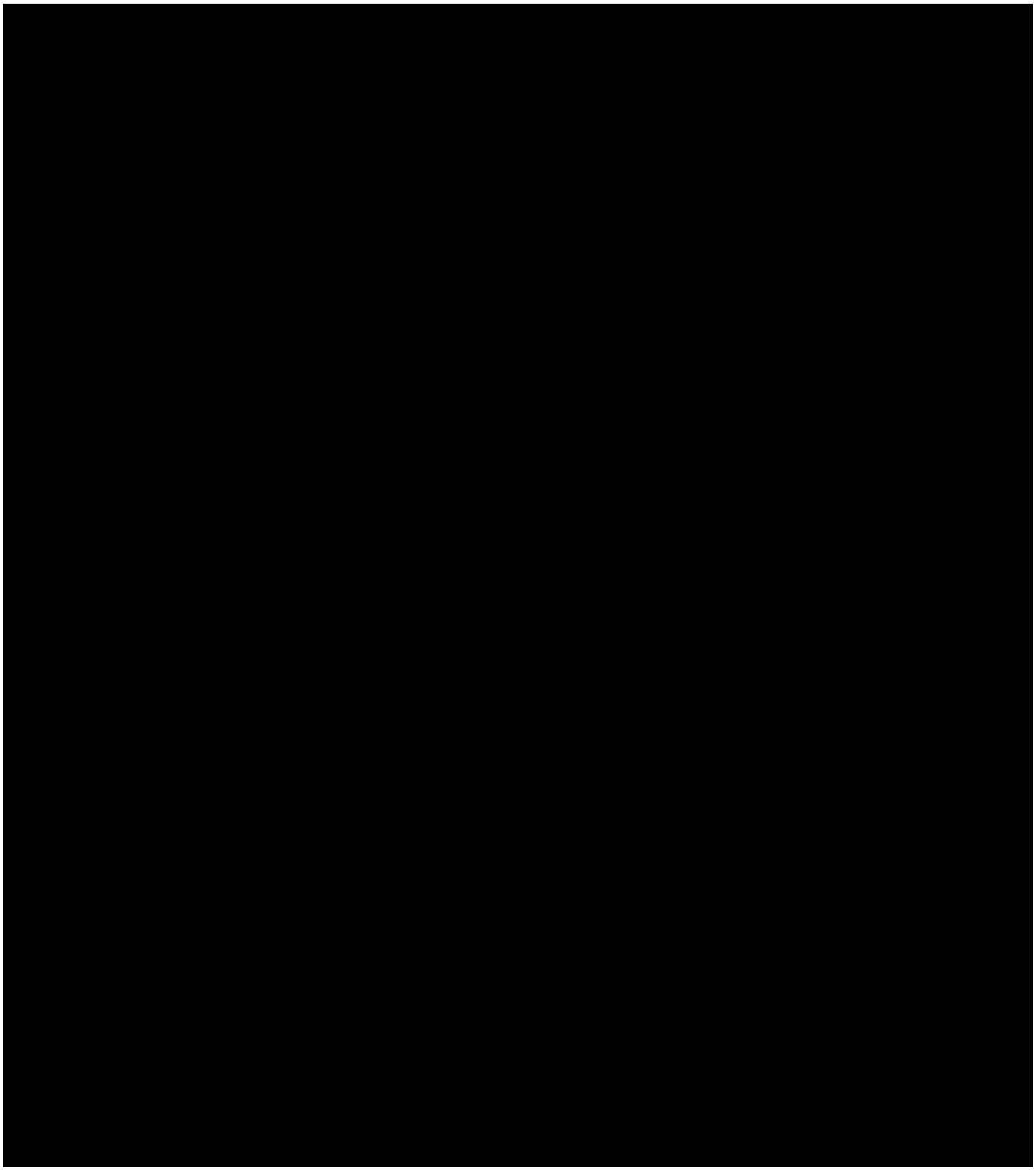
10.7.10 5-level EuroQol 5-dimensional questionnaire (EQ-5D-5L)

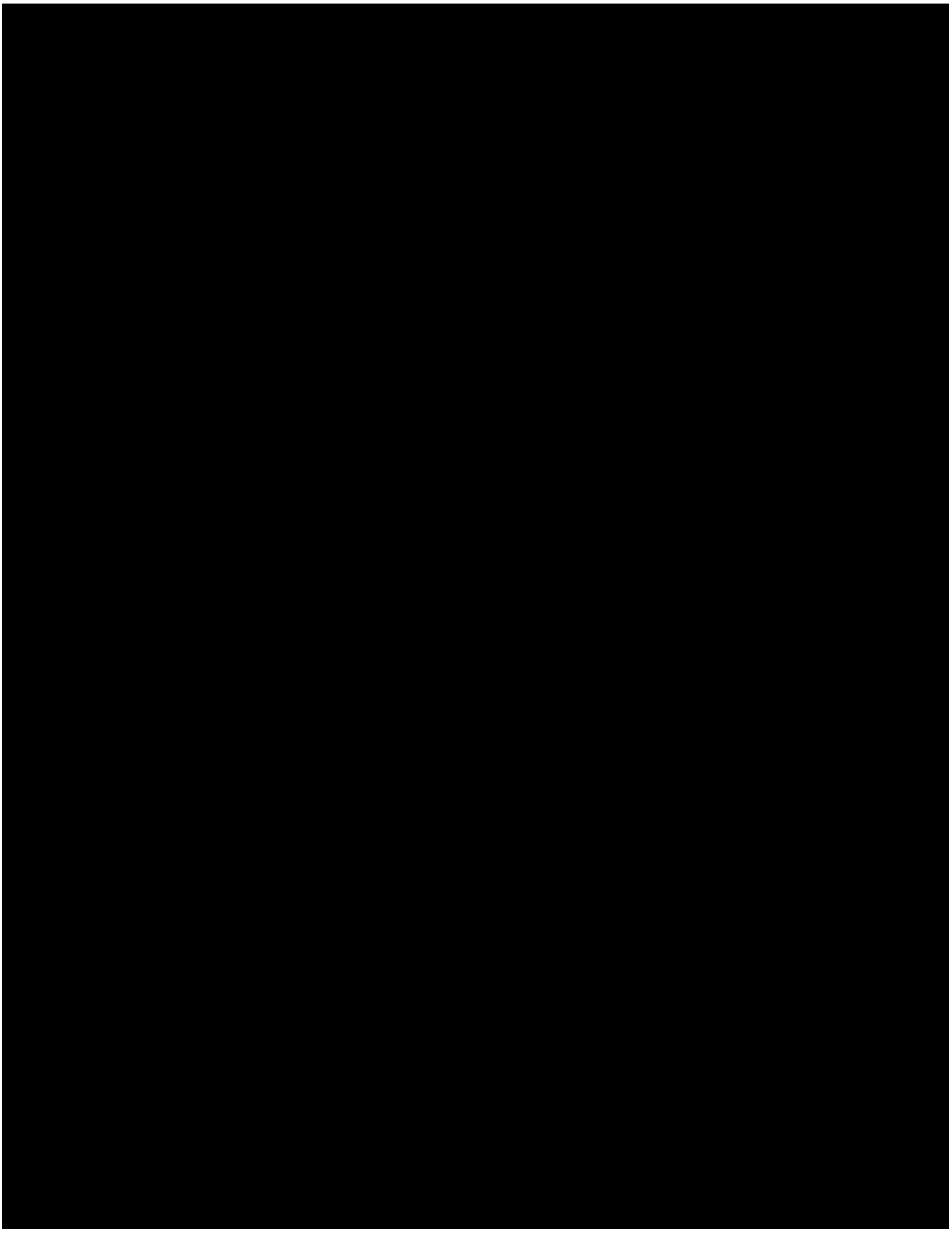
[redacted]



Disclaimer: *This is a preview of the EQ-5D instrument. It demonstrates the text, questions and response options included in this version. This preview does not represent the final product and should not be used as an official EQ-5D instrument.*

10.7.11 Missed school/work days





10.8 APPENDIX 8: DEFINITION OF ANAPHYLAXIS

"Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death (37)".

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.

10.9 APPENDIX 9: 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
- NonTB mycobacteria
- Pneumocystis pneumonia

This list is indicative and not exhaustive.

10.10 APPENDIX 10: LIST OF PROHIBITED LIVE ATTENUATED VACCINES

- Bacillus Calmette-Guérin (BCG) antituberculosis 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.

10.11 APPENDIX 11: COUNTRY-SPECIFIC REQUIREMENTS

10.11.1 Amendment for Japan

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

Use of H1-AH antihistamines for CSU treatment

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

All participants entering the study will be on up to 2-fold the approved dose of the non-sedating H1-AH. Participants will continue to take the same daily maintenance dose throughout the study unless they experience a flare, in which case rescue therapy may be initiated.

Rescue therapy

All participants on the approved non-sedating H1-AH dose (maintenance dose used at screening) will be allowed to take additional doses of their H1-AH 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-AH to the maximum allowed dose, participants can take a short course of OCS as rescue therapy during the treatment and follow-up periods.

The participants on maintenance dose of 2-fold the approved H1-AH dose will be allowed to take a short course of OCS as rescue therapy during the treatment and follow-up periods.

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 initial maintenance antihistamine dose should remain stable throughout the study, and participants should continue their maintenance dose once rescue treatment is no longer required.

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-AH and OCS including safety precautions please refer to the National Product labeling.

10.11.2 Amendment for France

Section 5.1 **Inclusion criteria** (See Section 5.1).

Children aged ≥6 to <12 years will not be recruited in France.

Additionally, all references to the ≥6 to <12 years age group in this protocol will not be applicable in France.

10.12 APPENDIX 12: ABBREVIATIONS

AAS:	angioedema activity score
AAS7:	angioedema activity score over 7 days
ADR:	adverse drug reaction
AEs:	adverse event(s)
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
CDLQI:	children's dermatology quality life quality index
CIU:	chronic idiopathic urticaria
COVID-19:	Coronavirus disease 2019
CRF:	case report form
CRSwNP:	chronic rhinosinusitis with nasal polyposis
CSU:	chronic spontaneous urticaria
CU-Q2oL:	chronic urticaria quality of life questionnaire
DLQI:	dermatology life quality index
DNA:	deoxyribonucleic acid
ECG:	electrocardiogram
eCRF:	electronic case report form

e-diary:	electronic diary
EoE:	eosinophilic esophagitis
EOS:	end of study
EOT:	end of treatment
EQ VAS:	EQ visual analogue scale
EQ-5D:	Euroqol-5 dimensions
EQ-5D-5L:	5-level EuroQol 5-dimensional questionnaire
EQ-5D-Y:	EuroQol 5-dimensional questionnaire youth
FcεRI:	Fc gamma receptor
GCP:	Good Clinical Practice
H1-AH:	H1-antihistamines
HBc Ab:	hepatitis B core antibody
HBs Ag:	hepatitis B surface antigen
HBV:	hepatitis B virus
HCV:	hepatitis C virus
HCV Ab:	hepatitis C virus antibody
HIV:	human immunodeficiency virus
HRQoL:	health-related quality-of-life
HSS7:	weekly hives severity score
IAF:	informed assent form
IB:	investigator's brochure
ICF:	informed consent form
ICH:	International Council for Harmonisation
IEC:	Independent Ethics Committee
IgE:	immunoglobulin E
IL:	interleukin
IL-13:	interleukin-13
IL-4:	interleukin-4
IL-4R:	interleukin-4 receptor
IMP:	investigational medicinal product
IRB:	Institutional Review Board
IRT:	interactive response technology
ISS7:	weekly itch severity score
IVIG:	intravenous immunoglobulin
IVRS:	interactive voice response system
IWRS:	interactive web response system
LTE4:	leukotriene E4
LTRA:	leukotrine receptor antagonist
mAb:	monoclonal antibody
MARCO:	Margin Consolidated
MID:	minimal important difference
NIMP:	non-investigational medicinal product
OCS:	oral corticosteroids
PD:	pharmacodynamics
PGDM:	prostaglandin D2 metabolite
PGIC:	Patient Global Impression of Change

PGIS:	Patient Global Impression of Severity
PRO:	patient-reported outcome
q4w:	every 4 weeks
qd:	once per day
RNA:	ribonucleic acid
SAE:	serious adverse event
SAP:	statistical analysis plan
SC:	subcutaneous
SoA:	schedule of activities
TB:	tuberculosis
Th2:	T-helper 2
UAS7:	weekly urticaria activity score
ULN:	upper limit of normal
WOCBP:	women of childbearing potential

10.13 APPENDIX 10: PROTOCOL AMENDMENT HISTORY

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

10.13.1 Amended protocol 01 (10 February 2020)

This amended protocol01 (Amendment 01) was considered to be nonsubstantial 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 was to incorporate recommendation from Japanese Institutional Review Boards (IRB) clinical trial review to align H1-antihistamines (H1-AH) medication intake for Japanese participants with the Japanese local guidelines for treatment of chronic spontaneous urticaria (CSU).

Protocol amendment summary of changes table

Section # and name	Description of change	Brief rationale
Table of Contents	Document History was added	As per request from the Japanese IRB during the review of the clinical trial application, the text is modified to be aligned with Japanese local guidelines for treatment of CSU. In Japan, patients with CSU who are not well controlled on approved H1-AH dose may escalate the H1-AH dose
4.1 Overall design	Modification of H1-AH medicine intake for Japanese patients: Reference provided to Section 10.11 that describes Local Japanese requirements	
6.5 Concomitant therapy	Reference provided to Section 10.11 that describes Local Japanese requirements	
6.5.1 Rescue medicine	Reference provided to Section 10.11 that describes Local Japanese requirements	

Section # and name	Description of change	Brief rationale
10.11 Appendix 11: Country-Specific Requirements	Rescue therapy with H1-AH is modified for Japanese patients. H1-AH that is used as background therapy can be increased during time of flare to 2-fold only. If the symptoms persist or if the participant is already on a baseline 2-fold the approved dose of H1-AH at time of flare, the patient can only be rescued by a short course of oral corticosteroids (OCS). No further increase in H1-AH is allowed.	only up to 2-fold the approved dose as per local guidelines.

10.13.2 Amended protocol 02 (30 April 2020)

This amended protocol 02 (Amendment 02) 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 increase the sample size of Study A (omalizumab naïve population) based on recommendation from Food and Drug Administration (FDA) to power the studies using conservative assumptions with regards to treatment effect and variability and to include children aged ≥6 to <12 years (for Study A only), and to switch the primary and the key secondary endpoints to establish the weekly urticaria activity score (UAS7) as the primary endpoint for European Union (EU) and EU reference countries based on recommendations from European Medicines Agency (EMA).

Protocol amendment summary of changes table

Section # and name	Description of change	Brief rationale
Title page	NCT and WHO identifiers were added.	This change is to add administrative details.
1.1 Synopsis 3. Objectives and endpoints	In the primary objective, "adult and adolescent participants with CSU" was changed to "study participants".	This change is to simplify the wording of the primary objective with population of adults, adolescents and children aged ≥6 to <12 years included in the primary analyses.
1.1 Synopsis 3. Objectives and endpoints 3.1 Appropriateness of measurements 4.2 Scientific rationale for study design 9.1 Statistical hypotheses 9.4.1 Efficacy analyses	1. The primary endpoint was changed for EU and EU reference countries as follows: "For EU and EU reference countries only: Change from baseline in weekly urticaria activity score (UAS7, composite patient reported itch and hive score) at Week 24". 2. Change from baseline in ISS7 "at Week 24 (in EU and EU reference countries)" was changed to key secondary endpoint for EU and EU reference countries.	According to EMA Scientific Advice, UAS7 was appointed as the primary endpoint in the EU and EU reference countries.

Section # and name	Description of change	Brief rationale
1.1 Synopsis 1.3 Schedule of activities 3.Objectives and endpoints 8. Study assessments and procedures 8.1 Efficacy assessments 8.1.4 Dermatology life quality index and children's dermatology quality life quality index	The wording was modified for Children's Dermatology Life Quality Index (CDLQI) lower age limit from ≥6 to <16 years old as follows: "CDLQI in patients ≥6 to <16 years old at Week 12 and Week 24". The following text was added: "The same questionnaires as for adolescents aged <16 years will be used for children aged ≥6 to <12 years".	Patient's age is updated for the completion of CDLQI questionnaire due to inclusion of children aged ≥6 to <12 years (for Study A). They will use CDLQI as well as adolescents younger than 16 years. The CDLQI is a tool that has been validated in children.
1.1 Synopsis 6.3 Measures to minimize bias: Randomization and Blinding	The following wording was added: "and children ≥6 to <12 years of age. In addition, in children, the study is not blinded to dose regimen due to the different frequency of IMP administration (q4w versus q2w)".	The text was implemented due to the inclusion of children aged ≥6 to <12 years in the study.
1.1 Synopsis 1.2 Schema 4.1 Overall design 9.2 sample size determination	The total anticipated number of participants across the 2 studies changed from "184" to "approximately 234" randomized participants. The number of participants per study arm required for the sample size estimate for Study A changed from "40" to "65", the overall number of participants for Study A changed from "80" to "130". The following terms "and up to approximately 5% of participants enrolled will be children ≥6 to <12 years of age (both children and adolescents recruited in some selected countries)" were added.	Based on the changes in sample size estimate and inclusion of children aged ≥6 to <12 years, the sample size increased from 40 to 65 participants per arm for Study A.
1.1 Synopsis 4.1 Overall design 5.1 Inclusion criteria (I 07.)	In the definition of the omalizumab incomplete responders, the term "at least" was added before the dose of omalizumab, and the wording was changed to "Omalizumab incomplete responders are defined as participants treated with at least 300 mg (q4w) omalizumab for at least 3 months (minimum of 3 injections) and who have had an inadequate response resulting in omalizumab discontinuation, as confirmed by Investigator assessment".	This is to clarify that patients, intolerant or with incomplete response to omalizumab, who took omalizumab doses higher than 300 mg are also eligible for the study.
1.1 Synopsis 1.2 Schema 2.1 Study rationale 4.1 Overall design 4.3 Justification for dose 6.1.1 Investigational medicinal product(s)	The following wording was added: - "Study A: Children ≥6 to <12 years of age: 200 mg q2w for children ≥30 kg at screening and 300 mg q4w for children <30 kg and ≥15 kg at screening". The dose regimen was changed by adding "q4w" for dupilumab and placebo, as follows: "1 injection q2w/q4w after an initial loading dose (2 injections) on Day 1".	The new text was implemented to reflect inclusion of children aged ≥6 to <12 years in the Study A only. Different schemes of IMP administration will be used in children depending on their weight (≥30 or <30 kg and ≥15 kg).
1.1 Synopsis 4.1 Overall design 6.3 Measures to minimize bias: Randomization and Blinding	The randomization was changed to the following wording: "The randomization will be stratified first by age (adults versus adolescents versus children in Study A and adults versus adolescents in Study B; up to approximately 5% of total sample size for children in Study A and approximately 5% of total sample size for adolescents in Studies A and B, separately). In adults, randomization will be stratified further by country. In adolescents/children ≥6 to <12 years of age, randomization will not be stratified further".	This is to clarify the stratification of the randomization by age with 3 strata for Study A (adults, adolescents and children) and 2 strata in study B (adults and adolescents).

Section # and name	Description of change	Brief rationale
1.1 Synopsis 4.1 Overall design 6.3 Measures to minimize bias: Randomization and Blinding	It is anticipated that approximately 30%-40% of enrolled participants will have angioedema.	This is to clarify that it is intended to enroll approximately 30-40% of patients with angioedema in the study in order to have a sufficient number of patients to assess effect of study intervention on CSU with angioedema.
1.1 Synopsis 9.2 Sample size determination	The following wordings were added to the sample size determination for study A: "An effect size of 0.7 or higher is assumed. An absolute change of 5 in ISS7 score is considered the minimal clinically important difference (MCID) and an absolute change of 10 in UAS7 score is considered the MCID. Based upon an SD of 7, a change of 5 in the ISS7 would correspond to an effect size of approximately 0.7. Based upon an SD of 14, a change of 10 in the UAS7 would correspond to an effect size of approximately 0.7. Based on this assumption, plus the assumption of a 15% dropout rate and inclusion of children, it is estimated that 65 patients per group will provide 96% power to detect an effect size of 0.7 or higher between the dupilumab arm and placebo using a 2-sided t-test with alpha = 0.05. This sample size estimate applies to both ISS7 (primary endpoint for all countries except EU and EU reference countries) and UAS7 (primary endpoint for EU and EU reference countries)." UAS7 was added in the sample size section for study B. The following wording was added "and an absolute change of 10 in UAS7 score is considered the MCID". "Based upon an SD of 14, a change of 10 in the UAS7 would correspond to an effect size of approximately 0.7". "This sample size estimate applies to both ISS7 (primary endpoint for all countries except EU and EU reference countries) and UAS7 (primary endpoint for EU and EU reference countries)." The text was amended to provide specific information on statistical considerations towards UAS7 score for A and B studies. Statistical considerations were updated. The power of the study changed from "90%" to "96%".	The text was aligned with the primary purpose of the amendment. The text was also amended to provide specific information on statistical considerations towards UAS7 score for A and B studies.
1.1 Synopsis 9.4.1 Efficacy analyses	The following covariate "presence of angioedema at baseline" was added to the primary endpoint analysis.	The analysis of covariance will take this covariate into account.
	"By baseline disease severity, presence of angioedema at baseline" were added to the Cochran-Mantel-Haenszel (CMH) test as covariates for adjustment. "The baseline disease severity will be defined according to UAS7 <28 and ≥28" was added. The wording "the corresponding baseline value, presence of angioedema at baseline" was added as covariates of the time-to-event endpoints analysis using the Cox proportional hazards model.	Covariate and cut-off selections were added to clarify the analysis of secondary endpoints, such as responder and time-to-event endpoints.
1.1 Synopsis	The wording "including UAS7 and HSS7" was added after "The same principle will be applied to handle the missing data for all of the weekly outcomes".	Missing data handling section was amended to indicate that such an approach also applies to UAS7 and HSS7.

Section # and name	Description of change	Brief rationale
1.3 Schedule of activities	In-clinic UAS at V1 and V2 was deleted.	In-clinic UAS assessment at pre-defined time points for confirmation of eligibility is considered less relevant for chronic spontaneous urticaria (CSU), a condition known with high fluctuating disease activity. E-diary based UAS7 baseline assessment is considered sufficient measure for evaluation of disease severity.
1.3 Schedule of activities	The following terms "except (for study A) for children <30 and ≥15 kg where it will be administered every 4 weeks. The planned last dose is at Week 22 except (for study A) for children <30 kg and ≥15 kg where it will be administered at Week 20" were added to the IMP administration.	The text was added to implement information on dosing for children aged ≥6 to <12 years.
	Following footnote was added in the table of Schedule of activities: "[b] Participants who discontinue the study treatment prematurely (prior to completing the 24-week treatment period) will perform the end of treatment (EOT) assessments at the time of discontinuation to assure a complete clinical assessment in close temporal proximity to the premature termination of study treatment. In addition, to allow assessment of participant outcomes over the stipulated study period, participants will be asked and encouraged to complete all remaining study visits and participate in all assessments according to the visit schedule". The alphabetical presentation of footnotes changed, ie, numbering of footnotes from "b" onwards was updated accordingly.	The text was added to implement information on patients who prematurely discontinue the study.
	Following footnote was changed in the table of Schedule of activities from "[b] Loading dose: 600 mg (2 SC injections) for 300 mg every 2 weeks (q2w) regimen for adults and adolescents ≥60 kg OR 400 mg (2 SC injections) for 200 mg q2w for adolescents <60 kg" to "[c] Loading dose on Day 1 of 600 mg (2 SC injections of 300 mg) followed by 300 mg every 2 weeks (q2w) regimen for adults and adolescents ≥60 kg OR 400 mg (2 SC injections of 200 mg) followed by 200 mg q2w for adolescents <60 kg and children ≥30 kg (Study A) OR 600 mg (2 SC injections of 300 mg) followed by 300 mg q4w for children <30 kg and ≥15 kg (Study A) OR matched placebo".	The text was added to implement information on dosing.
1.3 Schedule of activities 3. Objectives and endpoints 8. Study assessments and procedures 8.1.7 EuroQOL 5 dimensions questionnaire	The following terms "5-level EuroQol 5 dimensional questionnaire [EQ-5D-5L] [≥16 years old], EuroQol 5-dimensional questionnaire youth [EQ-5D-Y] [≥6 to <16 years old]" were added as regards with questionnaires completed for children.	The text was added to implement information on completion of questionnaires for children aged ≥6 to <12 years. The EQ-5D Youth version (EQ-5D Y) will be administered to children ≥6 to <12years old and adolescents 12 to 15 years old.
1.3 Schedule of activities 8.2.2 Vital signs	The wordings for vital signs were changed to "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)".	Oral temperature measurement is also allowed as this method is widely used in clinical trials.

Section # and name	Description of change	Brief rationale
1.3 Schedule of activities 10.2 Appendix 2: CLINICAL LABORATORY TESTS	The following footnote "i" was amended to: "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".	This is to simplify the wording for the serological status analysis and interpretation.
1.3 Schedule of activities	The following wording "a specific written informed consent" was changed to "consent" on footnotes "l to p".	Wording is changed to allow flexibility for country specifications and to be aligned with global informed consent form (ICF).
1.3 Schedule of activities	The following wording was added in the footnote "r": "For participants (with exception of adolescents and children) who decide to participate and provide consent for the photography, photographs will be taken of a representative area of CSU involvement for commercial activities. Instructions for taking the photographs are provided in the photography reference manual."	This is to clarify that CSU photographs representative area for commercial activities will be taken at selected sites at selected countries at baseline, Week 12, Week 24 and follow-up visit.
2.3 Benefit/risk assessment	The following sentence was added: "Moreover, in the AD pivotal trial submitted for registration to the US and EU, the efficacy and safety of dupilumab in children aged ≥6 to <12 years old with AD was comparable to that in older patients".	This is to clarify the positioning of dupilumab in children aged ≥6 to <12 years.
	The following paragraph was added: "Based on clinical studies in AD, the safety profile in pediatric patients (aged ≥6 to <12 years) appears similar to that of adults and adolescents with AD. As of 28 September 2019, 386 children aged ≥6 to <12 years had been exposed to dupilumab in AD clinical trials, with a total of 339.8 person-years of exposure".	This is to implement information on experience with dupilumab in children aged ≥6 to <12 years in pediatric studies in the AD indication.
4.3 Justification for dose	The following wording was added "The doses proposed for children ≥6 to <12 years of age are the dose regimens for the same age for AD, which have been submitted to the Health Authorities and are currently in review".	The text was added to implement information on dosing for children aged ≥6 to <12 years.
5.1 Inclusion criteria	I.01 Inclusion criterion was changed to: "Study A: Participant must be ≥6 years to 80 years of age at the time of signing the informed consent. Study B: Participant must be ≥12 years (or the minimum legal age for adolescents in the country of the investigational site) to 80 years of age at the time of signing the informed consent". Note: For those countries where local regulations do not permit enrollment of children aged ≥6 to <12 years of age, the recruitment will be restricted to those who are ≥12 years of age (or the minimum legal age for adolescents in the country of the investigational site). For those countries where local regulations do not permit enrollment of children aged ≥6 to <12 years and adolescents, the recruitment will be restricted to those who are ≥18 years of age.	This is to clarify participants' age for each study at the time of signing the informed consent. The criterion was changed for Study A since children aged ≥6 to <12 years are newly eligible. Participation of children in each country is made voluntary and depends on local country regulations, Health Authorities and IRB/EC approval.
	I.06 Inclusion criterion "In clinic UAS>4 prior to randomization (at V1 or V2)" was deleted.	In-clinic UAS assessment at pre-defined time points for confirmation of eligibility is considered less relevant for CSU, a condition known with high fluctuating disease activity. E-diary based weekly UAS7 baseline assessment is

Section # and name	Description of change	Brief rationale
		considered sufficient measure for evaluation of disease severity.
	The inclusion criterion I.10 was changed to "Participants ≥6 and <18 years of age must provide written informed assent, and their parent(s)/caregiver(s)/legally authorized representative(s) must sign the specific ICF. In countries where legal age of majority is >18 years, a specific ICF must also be signed by the participant's legally authorized representative".	This is to clarify that both the child and adolescent must provide written informed assent and the parent(s)/caregiver(s)/legally authorized representative(s) must sign the specific ICF.
5.2 Exclusion Criteria	The wording changed to "weight is less than 30 kg in adults and adolescents and 15 kg in children aged ≥6 to <12 years" on E01.	The E01 criterion is updated. The weight limit of <30 kg continues to be applicable for adults and adolescents. In Study A the children aged ≥6 to <12 years have a lower limit for inclusion of 15 kg.
	The wording "and during the screening period" was added to the exclusion criterion E08.	The E08 criterion is updated. Patients who had also significant infections during the screening period are not eligible.
	Omalizumab washout period was amended from 5 to 4 months before screening visit (V1).	The E17 criterion is updated to reflect 5 half-lives of omalizumab in CSU patients as per omalizumab label. The decrease in waiting period also provides a potential treatment option with the study medication for patients with a high medical need.
6.1.1 Investigational medicinal product	The intervention name details were updated and changed to: "For adults and adolescents ≥60 kg: Dupilumab 300 mg (q2w) For adolescents <60 kg and children ≥6 to <12 years of age ≥30 kg: Dupilumab 200 mg (q2w) For children ≥6 to <12 years of age <30 kg and ≥15 kg: Dupilumab 300 mg (q4w)". Similar changes were made for the placebo matching dupilumab 200 mg/300 mg. For dupilumab, the following terms were added: "300 mg every 28 ±3 days after an initial loading dose of 600 mg". The text was aligned for placebo. The following terms "or 28 ±3 days (Q4W) for children <30 kg and ≥15 kg" were added to the IMP administration.	This is to clarify study interventions administered and dosage levels for the pediatric population.
	"Drug visits" were replaced by "drug administrations".	Minor correction is made.
	The following wording is added: "For children ≥6 to <12 years, no self-administration of IMP is allowed by the participant, but parent(s)/caregiver(s)/legally authorized representative(s) who are trained by the Investigator or designee to prepare and administer IMP may perform home administration of IMP".	This is to clarify that home administration of IMP will be performed by parent(s)/caregiver(s)/legally authorized representative(s) for children ≥6 to <12 years.
7.2 Participation discontinuation/withdrawal from the study	The following wording was added "or if his/her parent(s)/caregiver(s)/legally authorized representative(s) decide to do so". "Parent(s)/caregiver(s)/legally authorized representative(s)" was added to "participants".	This is to clarify that caregiver(s)/legally authorized representative(s) can withdraw consent for children/adolescent patients.

Section # and name	Description of change	Brief rationale
8. Study assessments and procedures	The following wording was added: "In light of the public health emergency related to COVID-19 (Coronavirus disease 2019) (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."	This is to describe alternative temporary mechanism that can be implemented in the study conduct in case of pandemic requiring public health emergency eg, COVID-19.
8. Study assessments and procedures 8.1 Efficacy assessments	The following terms were added: "Parent(s)/caregiver(s)/ legally authorized representative(s) should not select any of the response choices on behalf of their child". "Patient(s)/parent(s)/caregiver(s)/legally authorized representative(s)" were added to "participant(s)".	This is to clarify that adolescents as well as children may be helped by their parents/caregivers for the reading and the understanding of the instructions before the completion of questionnaires, and that parents/caregivers will not answer instead 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 168 mL" (instead of 209 mL). "The maximum amount of blood collected expected as per schedule of activities from each adolescent over the duration of the study will not exceed 101 mL" (instead of 100 mL). The following wording was added for children aged ≥6 to <12 years: "The maximum amount of blood collected from each child will be compliant with the European guideline (27). The maximum amount of blood collected per each visit from each child aged ≥6 to <12 years will not exceed 11 mL per visit and the total maximum amount of blood collected expected as per schedule of activities for each child over the duration of the study will not exceed 47 mL".	Standard blood volumes were corrected for the study.
8.5.1.2 Handling procedures	Blood sample volume of 2 mL was added for children aged ≥6 to <12 years.	This is to specify the volume of blood taken from children ≥6 to <12 years of age that is lower than that of adults and adolescents.
9.1 Statistical hypotheses	The statistical hypotheses changed from "for comparing dupilumab 300 mg q2w against placebo" to "for comparing dupilumab".	The "300 mg q2w" was deleted here as "dupilumab" also included 200 mg q2w dose for adolescents <60 kg.

Section # and name	Description of change	Brief rationale
9.4.3 Other analyses	The following wording was added: "Data collected regarding the impact of the COVID-19 or other pandemics, on the patients will be summarized (eg, discontinuation due to COVID-19). Any additional analyses and methods required to investigate the impact of COVID-19 or other pandemics pandemic requiring public health emergency on the efficacy (eg, missing data due to COVID-19) and safety will be detailed in the SAP".	This is to describe alternative temporary mechanism that can be implemented in the study conduct in case of pandemic requiring public health emergency eg, COVID-19.
10.1.3 Informed consent process	The following wording was deleted: "A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative". The following wording was added: "• All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand. • It is the responsibility of the Investigator or designee (if acceptable by local regulations) to obtain written informed assent form (IAF) from each participant ≥6 years of age, and written ICF from each participant's parent(s)/caregiver(s)/legally authorized representative(s), prior to the participant's participation in the study, and prior to initiating any screening procedures. The written IAF/ICF should be signed and dated by the participant(s) and parent(s)/caregiver(s)/legally authorized representative(s), respectively. • The ICF and possibly the IAF used by the Investigator for obtaining the informed consent of the participant and parent(s) or the participant's legally acceptable representative must be reviewed and approved by the Sponsor prior to submission to the appropriate IRB/IEC for approval/favorable opinion. • For the children/adolescents' participation, local law must be observed in deciding whether one or both parents/ legally authorized representatives' consent is required. If only one parent or legally authorized representative signs the consent form, the Investigator must document the reason for only one parent or legally authorized representative's signature. • In addition, children/adolescents will assent as detailed below or will follow the Ethics Committee (IRB/IEC) approved standard practice for pediatric participants at each participating center (age of assent to be determined by the IRBs/IECs or be consistent with the local requirements): - Participants who can read the IAF will do so before writing their name and dating or signing and dating the form. - Participants who can write but cannot read will have the IAF read to them before writing their name on the form. • The original of each completed IAF/ICF must be retained by the Investigator as part of the participant's study record and a copy of the signed assent/consent form must be given to the participant/participant's parent(s)/caregiver(s)/legally authorized representative(s)".	Informed consent form section was adapted for children.

Section # and name	Description of change	Brief rationale
	The wording as regards to ICF was amended as follows: "For adults only, adults will have the option to provide consent for the use of remaining mandatory samples as well as any remaining additional serum/plasma samples for optional exploratory research".	Wording is changed to allow flexibility for country specifications and to be aligned with global ICF.
10.3 Appendix 3: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING Recording and follow-up of AE and/or SAE	"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 Sponsor." was replaced by "In such case, care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the study are properly mentioned on any copy of a source document provided to the Company".	The amended text was aligned with internal new process for the management of complementary source documents in the scope of the Safety Data Flow improvement program, in order to minimize the transfer of personal data to be compliant with the General Data Protection Regulation (GDPR), and harmonize processes across countries.
10.13 Appendix 10: Protocol Amendment History	The overall rationale and table with summary of changes for Amended protocol 01 were moved from the Cover page to Section 10.13.	This is aligned with Sanofi procedures.
10.12 Appendix 12: Abbreviations	IAF was added in the list of abbreviations.	IAF was added as the ICF section was adapted for children.
11. References	Reference No. 1 was newly added. The following reference was deleted: "Saini SS, Bindslev-Jensen C, Maurer M, Grob JJ, Baskan EB, Bradley MS, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 Antihistamines: A randomized, placebo-controlled Study. J Invest Dermatol. 2015;135(1):67-75", and the referencing numbering was updated accordingly.	The list of references was updated to refer the maximum amount of blood collected from children per visit and as per schedule of activities according to the European guideline.
Global	Minor edits and typo fixes were made.	This is to improve clarity.
	The wording "Children" was added to "adolescents".	This is for consistency with the study design.

10.13.3 Amended protocol 03 (09 October 2020)

This amended protocol 03 (Amendment 03) was considered to be nonsubstantial 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 was to address requirement of the French Ethic Committee to clearly specify in the protocol that children aged ≥6 to <12 years would not be recruited in France (see Appendix 11, Section 10.11.2 for specifics).

Protocol amendment summary of changes table

Section # and name	Description of change	Brief rationale
1.1 Synopsis	"In some selected countries" was added next to inclusion of children (≥6 to <12 years) in the study.	As per request from the French Ethic Committee, the wording is modified to specify that children aged ≥6 to <12 years will not participate in the study in France.
5.1 Inclusion Criteria	For inclusion criterion I.01, reference provided to Appendix 11 (Section 10.11.2) that describes Local French requirements was added.	
10.11.2 Amendment for France	Inclusion criterion I01 is modified for French participants to exclude participation of children aged ≥6 to <12 years, and a blanket statement is provided which confirms that all references to the ≥6 to <12 years age group in this protocol will not be applicable in France.	

10.13.4 Amended protocol 04 (29 April 2021)

This amended protocol 04 (Amendment 04) 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

EFC16461 is a double-blind placebo controlled phase 3 study in patients with chronic spontaneous urticaria (CSU) who remain symptomatic despite the use of H1 antihistamine treatment, composed of Study A conducted in patients naïve to omalizumab and Study B in patients who are intolerant or incomplete responders to omalizumab.

There is no change to the Study A conduct or analysis plan.

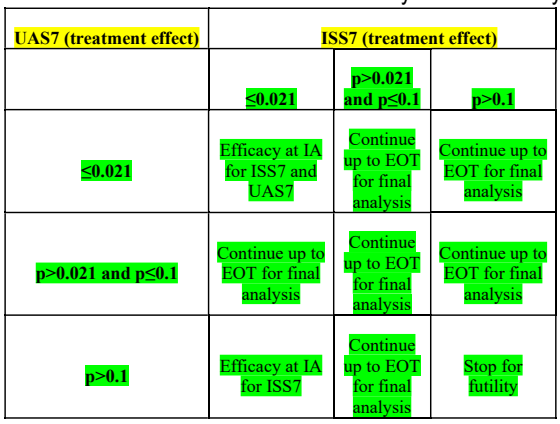
The primary purpose of this amendment is to plan for an interim analysis for Study B when 80 randomized participants would have completed their 24-week treatment period.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Front page	Sponsor name and address added	These were missing in amended protocol 03
Section 1.1 Synopsis - Number of participants	Added: An interim analysis will be performed when the first 80 randomized patients would have completed their 24-week treatment period, by the interim analysis cut-off date.	Due to COVID impact and associated difficulties to enroll patients in Study B (intolerant or incomplete responders to omalizumab), an interim analysis of Study B will be performed to allow an earlier assessment of efficacy or stop for futility in this population. This protocol amendment describes the details of this interim analysis with possible scenarios for study discontinuation for considering efficacy, continuation or stopping the study. Blinding and integrity of the study will be ensured by appropriate measures.
Section 1.1 Synopsis - Sample size calculations	Added: Considering the reduced drop-out rate of 10% observed during the study, an interim analysis will be performed when the first 80 randomized patients would have completed their Week 24 visit by the interim analysis cut-off date. Using the O'Brien-Fleming approach with information fraction 0.77 and overall type-I error controlled at 0.05, the alpha spending at this interim analysis will be 0.021, and the alpha spending at the final analysis when all 104 patients complete the study will be 0.043. At the Study B interim analysis, it is estimated that 40 patients per group will provide 74% power to detect a treatment effect of 5 or higher with SD 7 and minimal detectable difference (MDD) of approximately 3.8 for ISS7 and a treatment effect of 10 or higher with SD 14 and MDD of approximately 7.6 for UAS7 between the dupilumab arm and placebo using a 2-sided t-test with alpha = 0.021. With the decision process outlined in section 9.5, the overall power for the study will be approximately 88%. Updated: The sample size calculations and the alpha spending by O'Brien-Fleming approach were calculated by nQuery Advisor and nTerim 4.0.	
Section 1.1 Synopsis Analysis population	Added: For Study B interim analysis, the primary analysis population will be the intent-to-treat24 (ITT24) population, defined as all patients who were randomized at least 24 weeks before the interim analysis cut-off date and would have completed the Week 24 visit by the cut-off date of interim analysis.	
Section 1.1 Synopsis Multiplicity considerations	Updated: Within each study, Study A (omalizumab naïve) and Study B (omalizumab intolerant or incomplete responders), the multiplicity procedure is proposed to control the overall Type-I error rate for testing the primary endpoint and the key secondary endpoints. Detailed hierarchical testing procedure will be defined in the study SAP.	

Section # and Name	Description of Change	Brief Rationale
	Added: Study A is considered positive when the primary endpoint achieves statistical significance with 2-sided significance level 0.05. At the interim analysis, the study B is considered positive when the primary endpoint achieves statistical significance using 2-sided significance level 0.021. If Study B meets the criteria to continue at the interim analysis, at the final analysis of Study B, it will be considered positive when the primary endpoint achieves statistical significance using 2-sided significance level 0.043. Multiplicity adjustment for the other efficacy endpoints will be described in the study SAP.	
Section 1.1 Synopsis Planned database lock date/interim analysis	Added in section title: /Interim analysis Added: In addition, an interim analysis will be performed for Study B when the defined ITT24 population data are available.	
Section 9.2 Sample size determination	Added: Considering the reduced drop-out rate of 10% observed during the study, an interim analysis will be performed when the first 80 randomized patients would have completed their Week 24 visit by the interim analysis cut-off date. Using the O'Brien-Fleming approach with information fraction 0.77 and overall type-I error controlled at 0.05, the alpha spending at this interim analysis will be 0.021, and the alpha spending at the final analyses when all 104 patients complete the study will be 0.043. At the Study B interim analysis, it is estimated that 40 patients per group will provide 74% power to detect a treatment effect of 5 or higher with SD 7 and minimal detectable difference (MDD) of approximately 3.8 for ISS7 and a treatment effect of 10 or higher with SD 14 and MDD of approximately 7.6 for UAS7 between the dupilumab arm and placebo using a 2-sided t-test with alpha = 0.021. With the decision process outlined in section 9.5, the overall power for the study will be approximately 88%. Updated: The sample size calculations and the alpha spending by O'Brien-Fleming approach were calculated by nQuery Advisor and nTerim 4.0.	
Section 9.3 Populations for analyses	Added in Table 5: the ITT24 population (for the Study B interim analysis). All participants who were randomized at least 24 weeks before the interim analysis cut-off date and would have completed the Week 24 visit by the cut-off date of interim analysis. The exact interim analysis cut-off date will be specified in the SAP, which will be finalized before the interim analysis.	
Efficacy	Updated in Table 5: The ITT population (ITT24 for Study B interim analysis).	
Section 9.4.1 Efficacy analysis	Added: For study B, an interim analysis will be performed using the O'Brien-Fleming approach with information fraction 0.77 and overall type-I error controlled at 0.05, the alpha spending at this interim analysis will be 0.021, and the alpha spending at the final analyses when all 104 patients complete the study will be 0.043. The decision process that applies to this interim analysis is outlined in Section 9.5.	

Section # and Name	Description of Change	Brief Rationale
Section 9.5 Interim analysis	Updated: No interim analysis is planned for Study A. For Study A, a primary database lock will be performed when all randomized participants have completed their treatment phase. Final analysis 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. Added: For Study B, an interim analysis (IA) will be performed when the first 80 randomized participants would have completed their 24-week treatment period by the interim analysis cut-off date. This interim analysis will use the O'Brien-Fleming approach with information fraction 0.77 and overall type-I error controlled at 0.05, with an alpha spending at the interim analysis of 0.021, and an alpha spending at the final analysis (when all 104 patients complete the study) of 0.043. The possible outcomes from this interim analysis are summarized below and in Table 8: **Efficacy at IA**: • In case p-value at interim analysis is ≤0.021 in ISS7 and UAS7, Study B is considered "Efficacy at IA for ISS7 and UAS7" (as shown in Table 8). • In case p-value at interim analysis is <=0.021 for ISS7 and >0.1 for UAS7, Study B is considered "Efficacy at IA for ISS7" (as shown in Table 8). In case of "Efficacy at IA", the cut-off date for the interim analysis will be considered as the primary database lock, the study treatment will continue, and a final database lock will occur when all participants have completed the last visit in the study. Additional data between this database lock and last participant completing last visit will be summarized in a CSR addendum. **Stop for futility**: • In case p-value at interim analysis is >0.1 for ISS7 and UAS7, Study B is considered "Stop for futility" (as shown in Table 8). In case of stop for futility, enrollment of additional patients will stop for Study B if 104 patients have not been enrolled and the study treatment will be stopped for all current participants. Additional data between this database lock and last participant completing last visit will be summarized in a CSR addendum. **Continue up to EOT for the primary analysis:** • For all other situations the decision is to continue the study (as shown in Table 8) until 104 patients (52 patients per group) complete the study treatment and the final analysis will be conducted with an alpha 0.043.	

Section # and Name	Description of Change	Brief Rationale
	In this case Study B will continue up to the EOT for the primary analysis, a second database lock will be performed when all randomized participants have completed their treatment phase and a final database lock will occur when all participants have completed the last visit in the study. Table with p values added, as Table 8 (Table 8 in amended protocol 03 becomes Table 9) Table 8: Possible outcomes from the Study B interim analysis.  To maintain study integrity with respect to the subsequent visits and analyses after the Study B interim analysis, a dissemination plan will be written. This plan will clearly identify two independent study teams and an independent committee (including a statistician). Details of the process will be described in the Study SAP. The independent committee will be in charge of analyzing and reviewing the interim analysis and providing guidance about the above described scenarios (continue, success or futility). Two independent study teams will be put in place. Specific steps will be setup to maintain the blind of the study to all individuals involved in the conduct of the study and/or analysis, and to protect the overall blinding and integrity of the study data, after the interim analysis has been performed. Details will be provided in the dissemination plan.	
Section 10 Supporting documentation and operational considerations	Section 10.13 was added	To include Protocol Amendment History for amended protocol 03

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