AMENDED CLINICAL TRIAL PROTOCOL 01

Protocol title:	**A multi-center, single-arm study to investigate the pharmacokinetics and safety of dupilumab in male and female participants ≥2 years to <12 years of age with uncontrolled chronic spontaneous urticaria (CSU)**
Protocol number:	**PKM16982**
Amendment number:	**01**
Compound number (INN/Trademark):	**SAR231893 dupilumab/Dupixent®**
Brief title:	**A study to investigate the pharmacokinetics and safety of dupilumab in participants ≥2 years to <12 years of age with uncontrolled chronic spontaneous urticaria (CSU)**
Acronym:	**LIBERTY-CSU CUPIDKids**
Study phase:	**Phase 3**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
Legal registered address:	**1 avenue Pierre Brossolette 91380 Chilly-Mazarin France**
Monitoring team's representative name and contact information	

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 01	All	31 May 2023, version 1 (electronic 2.0)
Original Protocol		30 March 2022, version 1 (electronic 1.0)

Amended protocol 01 (31 May 2023)

OVERALL RATIONALE FOR THE AMENDMENT

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

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page and throughout	Document updated to "Amended Clinical Trial Protocol 01"; summary of changes including rationale added. NCT number added.	Title page amendments made as per Sanofi standards.
	Updated all other formatting, header, etc, relating to protocol amendment, and corrected any formatting inconsistencies.	Formatting updated throughout as per Sanofi standards
Throughout the protocol.	Removed the population with chronic inducible cold urticaria and updated the study title accordingly.	Remove the inclusion of patients with CICU following the results of the Phase 3 study EFC16720, which evaluated the efficacy and safety of dupilumab in adult patients with CICU who remained symptomatic despite the use of H1-antihistamine treatment. This study did not meet the required efficacy endpoints to continue this program, including the development in the pediatric CICU population. Only pediatric participants with chronic spontaneous urticaria will be recruited in this study.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, Objectives and endpoints 3 Objectives, endpoints, and estimands	Deleted secondary objective "To assess the impact of dupilumab on urticaria activity in participants with CICU who remain symptomatic despite the use of H1-antihistamine or appropriate preventive measures" and related endpoints. Deleted footnote b.	These objective, endpoints and footnotes are specific to the chronic inducible cold urticaria patient group that is removed from the PKM16982 protocol.
1.3 Schedule of activities (SoA), Footnotes	Deleted footnotes h and q. The footnotes are renamed accordingly.	
5.1 Inclusion criteria	Deleted inclusion criteria I04 and I05. The text is replaced by "This criterion is deleted as per amendment 01".	These inclusion criteria are specific to the chronic inducible cold urticaria patient group that is removed from the PKM16982 protocol.
10.12 APPENDIX 12: Patient-reported outcomes and clinician-reported outcomes	Deleted subsections "10.12.4 Wheal Intensity Likert Scale" and "10.12.5 Acquired Cold Urticaria Severity Index".	These subsections are specific to the chronic inducible cold urticaria patient group that is removed from the PKM16982 protocol.
11 References	References cited in the subsections specific to the chronic inducible cold urticaria patient group are removed.	
Throughout the protocol.	Deleted "modified" from "modified ISS7" and "modified HSS7".	Correction of an error in the original protocol.
1.1 Synopsis, Number of participants, 3.1 Appropriateness of measurements, 4.1 Overall design, 6.3 Measures to minimize bias: randomization and blinding	Removed "The lower weight group includes 3 separate dose regimens (see "Treatment period" above)".	Correction of error in the protocol.
1.1 Synopsis, Statistical considerations, Primary endpoint 9.2.2 Primary endpoint(s) analyses	Removed "A population PK model will be developed using nonlinear mixed effect modeling to describe the PK profile of dupilumab. Pharmacokinetic parameters will be calculated using the population pharmacokinetic (PopPK) model and summarized using descriptive statistics."	A population PK model may be developed using nonlinear mixed effect modeling to describe the PK profile of dupilumab. The population PK analysis will be reported in a separated document.
8.4.2 Pharmacokinetics parameters	Removed "A PopPK model will be developed using nonlinear mixed effect modeling to describe the PK profile of dupilumab. The following PK parameters will be calculated, using the PopPK model."	
1.2 Schema; 1.3 Schedule of activities (SoA); Throughout the protocol	Removed the Week 4 visit. Visits at Week 1 and Week 2 merged to one visit; that is Visit 3A at Week 1 for half of the participants and Visit 3B at Week 2 for the other half. Visits 6, 7 and 8 are renumbered to 4, 5 and 6, respectively.	To reduce the burden of attending site visits for participants (to avoid missing school and work).
Throughout the protocol	Decreased the number of PK samplings. Participants will be assigned 1:1 to PK schedule A or B. Decreased the number of blood and urine tests.	To decrease pediatric patient burden by reducing the number of blood and urine tests and volume of blood taken.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities (SoA)	Added footnotes “s”: For participants assigned to PK Schedule A (determined by IRT system at Visit 2): Weeks 0, 1, 12, 24, 36, and “t”: For participants assigned to PK Schedule B (determined by IRT system at Visit 2): Weeks 0, 2, 12, 24, 36. Added cross references to “X” marks for visits 3A and 3B, respectively, in row “Serum PK samples for dupilumab concentration”. Removed “serum TARC” and urine biomarkers “LTE4/tPGDM/Creatinine”. Deleted “Spot urine collection should be done” from footnote “u”.	
2 Introduction	Deleted “Moreover, in CRSwNP studies, a decrease in urinary leukotriene E 4 (LTE4) and prostaglandin D 2 metabolite (PGDM) was reported”	
8.4.1.1 Sampling time	Added “Participants will be assigned by IRT system at Visit 2, 1:1, to PK schedule A (Weeks 0, 1, 12, 24, 36) or to PK schedule B (Weeks 0, 2, 12, 24, 36)”. Deleted “Special procedures for the collection, storage, and shipping of serum are described in separate operational manuals”.	
8.6 Biomarkers	Deleted from first bullet point: “and urine samples” and “serum thymus and activation-regulated chemokine (TARC) TARC, urine LTE4, and urine tetranor Prostaglandin D2 metabolite (tPGDM). Urine LTE4 and tPGDM results will also be reported per mg creatinine”. Deleted from second bullet point: “and urine”.	
1.3 Schedule of activities (SoA);	Added row “Prior and concomitant medications” and “X” mark in all visits. Added row “IRT attribution treatment” and “X” mark in Visits 2 and 4	Clarification.
1.3 Schedule of activities (SoA), Footnote j. 8.2.2 Vital signs	Deleted “oral, axillary, or tympanic” before “temperature (°C)” Deleted “Oral, axillary, or tympanic temperature measurement can be used” from the second bullet point.	No need to specify the method of measurement
1.3 Schedule of activities (SoA), Footnote l; 10.2 APPENDIX 2: Clinical laboratory tests, Table 9 - Protocol-required laboratory tests, row “Other screening tests”.	Added “HBV DNA, and HIV and HCV RNA samples for confirmation purpose will only be collected if a confirmation test is requested. The collection will be done during an unscheduled visit onsite”.	Consistency with PKM16982 study collection flow chart.
1.3 Schedule of activities (SoA), Footnote o. 3.1 Appropriateness of measurements; 8 Study assessments and procedures, Fifth bullet point	“Blood volume required is in accordance with Directive 2001/20/EC” changed to “Blood volume required is in accordance with blood sample in volumes in child health research”. Added citation for new reference “Howie 2011”. “The maximum amount of blood collected from each participant … will be compliant with Directive 2001/20/EC” changed to “The maximum amount of blood collected from each participant … will be compliant with Blood sample volumes in child health research”. Added citation for new reference “Howie 2011”. Removed citation for reference “European Commission website 2017”.	No EU countries included in this study. Added the US directive.

Section # and Name	Description of Change	Brief Rationale
8 Study assessments and procedures, Fifth bullet point	The text "…which specifies that pediatric blood sample volume should not exceed 1% of total blood volume (TBV) at any single time and 3% of TBV over 4 weeks. Overall, the maximum amount of blood collected from each participant… will not exceed approximately 20 mL, 34 mL, and 38 mL, respectively. The amount of blood collected from each… approximately 1.2 mL to 11.4 mL." updated to "…which specifies that pediatric blood sample volume should not exceed 1% to 5% of total blood volume (TBV) over 24 hours and up to 10% of TBV over 8 weeks. Overall, the maximum amount of blood collected from each participant …will not exceed approximately 18 mL, 22 mL, and 31mL, respectively. The amount of blood collected from …approximately 1.2 mL to 11 mL".	
2.3.1 Risk assessment	The text "Dupilumab has an extensive safety database. As of 28 September 2021 (Data Lock Point), 13 062 participants were enrolled into the development program for dupilumab and included in the safety population: 564 as healthy volunteers, 5011 from AD studies, 4091 from asthma studies, 782 from CRSwNP studies, 428 from eosinophilic esophagitis (EoE) studies, 103 from the grass allergy study, 173 from peanut allergy studies, 1214 from the chronic obstructive pulmonary disease (COPD) study, 309 from prurigo nodularis (PN) studies, 235 from the CSU study, 30 from the CICU study, 16 from the CRSwNP 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 8 from allergic fungal rhinosinusitis (AFRS) study. The number of participants exposed to dupilumab in clinical studies was 10565 (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, 118 in the CSU study, 15 in the CICU study, 8 in the CRSwNP study, 16 in the BP study, 10 in the ABPA study, 20 in the HFE study and 4 in the AFRS study)" changed to "Dupilumab has an extensive safety database including in pediatric patients aged ≥6 months to <18 years. As of 28 March 2022, 13 577 participants were enrolled into the development program for dupilumab and included in the safety population with 311 participants with urticaria. Updated data are available in the current Investigator's Brochure".	Wording was changed to clarify that the most up to date safety data are available in the current Investigator's Brochure.
11 References	Added reference "Howie SR. Blood sample volumes in child health research: review of safe limits. Bull World Health Organ. 2011 Jan 1;89(1):46-53" (1). Removed reference "European Commission website. Ethical considerations for clinical trials on medicinal products conducted with minors. Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use; 2017: 1-48. Available from: URL: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_09_18_ethical_consid_ct_with_minors.pdf".	No EU countries included in this study. Added the US directive.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion criteria	The inclusion criterion I02 “Participants who have a documented diagnosis of CSU or CICU >6 months prior to screening visit ” was updated to “Participants who have history of a diagnosis of CSU prior to screening (V1) or symptoms consistent with a diagnosis of CSU for at least 3 months in the Investigator’s opinion”. Deleted the word “consecutive” from inclusion criterion I03 “Participants with CSU (characterized by recurrent itchy wheals with or without angioedema for >6 consecutive weeks) who remain symptomatic at the time of screening despite regular H1-antihistamine treatment”.	To allow more flexibility to enroll participants.
1.1 Synopsis, Noninvestigational medicinal product(s); 6.1.1 Non investigational medicinal products	The text “During the study participants should continue… with a long acting non-sedating H1-antihistamine up to 4-fold the licensed dose for CSU… or may continue adhering to appropriate preventive measures with no H1-antihistamines intake (if applicable in a participant with CICU)” was updated to “It is recommended that participants continue …with a long acting non-sedating H1-antihistamines”.	To allow patients to have more flexible standard of care background therapy without requiring continuous high dose H1 antihistamine use.
6.1.1 Non investigational medicinal products	Added “Any change to H1-antihistamine therapy should be documented in the eCRF including the date of change as well as the dosage regimen”.	
1.3 Schedule of activities (SoA), Footnote g. 6.1 Study intervention(s) administered	Added “participant (if ≥12 years of age)” before “participants’ parent(s)/caregiver(s)/legally authorized representative” in footnote wording. Added “participant (if ≥12 years of age)” throughout this section. Added “Note: Participants <12 years of age are not permitted to perform any IMP self-administration. Participants ≥12 to <18 years of age, if trained, are permitted to perform IMP self-administration at home (except for injections in the upper arms) under the supervision of their trained parents/ legally authorized representatives/caregivers”. Added “and in the Patient User Instruction Manual” at the sentence “This training must be documented in the participant’s study file”.	Clarification about the age requirements for self-administration of the IMP and for the related training.
9.2.3.2 Immunogenicity analysis	Added “including neutralizing antibodies” to the sentence “The ADA analysis will be conducted on the ADA population.”	Clarification.
10.1.6 Dissemination of clinical study data	The “clinicalstudydatarequest.com” was replaced by “vivli.org”.	Change in the Sponsor's data sharing platform.
10.4.2 Contraception guidance	The cross reference to footnote “c” was removed.	Correction.
10.7 APPENDIX 7: Country-specific requirements	The text “During the study participants should continue… with a long acting non-sedating H1-antihistamine up to 2-fold the licensed dose; or may continue adhering to appropriate preventive measures with no H1-antihistamines intake (if applicable in a participant with CICU)” was updated to “It is recommended that participants continue … with a long acting non-sedating H1-antihistamine up to 2-fold the licensed dose”.	To allow patients to have more flexible standard of care background therapy without requiring continuous high dose H1-antihistamine use.

Section # and Name	Description of Change	Brief Rationale
10.13 APPENDIX 13: Abbreviations	Removed “ABPA: allergic bronchopulmonary aspergillosis”, “ACU: acquired cold urticaria”, “ACUSI: Acquired Cold Urticaria Severity Index”, “BP: bullous pemphigoid”, “CICU:chronic inducible cold urticaria”, “CIndu: Chronic Inducible Urticaria”, “ColdU: cold urticaria”, “COPD: chronic obstructive pulmonary disease”, “EoE: eosinophilic esophagitis”, “HFE: atopic hands and foot dermatitis”, “LTE4: leukotriene E 4”, “PGDM: prostaglandin D2 metabolite”, “PN: prurigo nodularis”, “PopPK: population pharmacokinetic”, “TARC: serum thymus and activation-regulated chemokine” and “tPGDM: tetranor Prostaglandin D2 metabolite”.	Consistency in the protocol.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

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

Brief title:

A study to investigate the pharmacokinetics and safety of dupilumab in participants ≥2 years to <12 years of age with uncontrolled chronic spontaneous urticaria (CSU).

Rationale:

Chronic urticaria is defined by the appearance of itchy wheals (hives) with or without angioedema for more than 6 weeks, for which no triggering factor is identified (2, 3, 4).

The pathologic mechanisms underlying chronic spontaneous urticaria (CSU), while not well understood, are thought to be shared and are largely driven by mast cell activation and degranulation. Degranulation 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. Interleukin (IL)-4/IL-13 signaling is required for antibody isotype switching to IgE production in B cells and contributes to mast cell survival and function (5, 6). Therefore, blockade of IL-4/IL-13 by dupilumab represents a potential novel therapeutic approach for CSU patients.

While antihistamines are the mainstay of therapy, up to 50% of patients may remain uncontrolled with antihistamines alone. Targeting IgE with omalizumab has been successful in treating CSU patients but not all patients are responsive to this therapy, nor is it approved for patients under 12 years of age. Treatment of pediatric patients with CSU remains challenging; the pathophysiology of this condition is thought to be the same across all age groups, thus antihistamines are first-line therapy. However, there remains a significant unmet need for novel therapies, particularly in the pediatric population.

Dupilumab is a fully human monoclonal antibody (mAb) directed against the interleukin-4 receptor alpha (IL-4Rα) subunit, 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 and has shown efficacy in multiple diseases with underlying Type 2 inflammation such as atopic dermatitis (AD), asthma, and chronic rhinosinusitis with nasal polyposis (CRSwNP). These data demonstrate dupilumab's potential to modulate other diseases thought to be driven by Type 2 inflammation such as CSU.

Currently the Sponsor is conducting a Phase 3 program with dupilumab for the treatment of CSU patients (EFC16461 composed of 2 parts, Study A and Study B) (see Section 2.1 and Section 2.2).

EFC16461 Study A was completed, demonstrating the efficacy of dupilumab and an acceptable safety profile in participants with CSU who remain symptomatic despite the use of H1-antihistamine treatment (see Section 2.3 for additional details). EFC16461 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.

The likelihood of a shared underlying Type 2 inflammatory mechanism across all ages in CSU, along with early positive findings supporting dupilumab for treatment of CSU in the omalizumab naive pediatric patient population support to further study this potential therapy in pediatric patients. Therefore, a clinical study will be conducted in children aged ≥2 to <12 years old with CSU to evaluate pharmacokinetics (PK) and safety in the CSU population.

Objectives and endpoints:

Objectives	Endpoints
Primary	
• To characterize the serum concentration of dupilumab over time	• Concentration of dupilumab in serum over time including C_{trough} at Week 12 and Week 24
Secondary	
• To assess the safety of dupilumab	• Safety and tolerability assessments: Incidence of TEAEs or SAEs
• To assess the immunogenicity of dupilumab	• Incidence of ADA to dupilumab over time
• To evaluate the improvement in health-related QoL in participants with CSU receiving dupilumab who remain symptomatic despite the use of H1-antihistamine	• Change from baseline in C-DLQI in children from 4 years to less than 12 years of age at Week 24 • Change from baseline in IDQOL in children from 2 years to less than 4 years of age at Week 24
• To assess the impact of dupilumab on urticaria activity, itch and hives severity scores in participants with CSU who remain symptomatic despite the use of H1-antihistamine	• Change from baseline in the modified UAS7[a] at Week 24 • Change from baseline in the ISS7 at Week 24 • Change from baseline in the HSS7 at Week 24

Abbreviations: ADA = antidrug antibodies; C-DLQI = Children Dermatology Life Quality Index; CSU = chronic spontaneous urticaria; C_{trough} = trough concentration; HSS7 = hive severity score over 7 days; IDQOL= Infant's Dermatitis Quality of Life Index; ISS7 = itch severity score over 7 days; SAEs = serious adverse events; QoL= quality of life; TEAEs = treatment-emergent adverse events; UAS7 = urticaria activity score over 7 days.

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

Overall design:

This is a Phase 3, multicenter, single-arm, 24-week treatment study assessing the PK and safety of dupilumab in participants ≥2 years to <12 years of age with CSU not adequately controlled with H1-antihistamine treatment.

The primary objective of this study is to characterize the PK profile and the secondary objective is to assess the safety profile of dupilumab in children aged ≥2 years to <12 years with uncontrolled CSU. This study will additionally collect clinical information regarding the response to treatment in this age group, however all efficacy analyses will be descriptive.

In this study, all enrolled participants will receive dupilumab injections in a weight/age-tiered dosing regimen for 24 weeks, followed by a 12-week post-treatment observational period at the end of the study intervention.

Brief summary:

This is a multicenter, single-arm, 24-week treatment, Phase 3 PKM16982 study.

The purpose of this study is to investigate the PK and safety of dupilumab in children diagnosed with CSU who remain symptomatic despite the use of H1-antihistamine treatment.

Study details include:

- Screening: 2 to 4 weeks.
- The treatment duration will be 24 weeks.
- Follow-up period: 12 weeks.
- The study duration will be 38 to 40 weeks (including screening and follow-up).
- The number of study visits will be 6.

Screening period:

Prior to screening, participants must be receiving treatment for CSU with a non-sedating H1-antihistamine.

Prior to all screening assessments, the participant and the parent(s)/caregiver(s)/legal guardian(s) must sign and date the Ethics Committee approved informed assent form (IAF) and informed consent form (ICF), respectively. The participant assent should be obtained for all participants ≥6 years of age (or above an age determined by the Institutional Review Board [IRB]/Independent Ethics Committee [IEC]).

All participant(s)/parent(s)/caregiver(s)/legal guardian(s) will receive information on the study objective(s) and procedures from the Investigator. If informed consent has been provided, participants will be assessed for inclusion and exclusion criteria. Blood will be collected for clinical laboratory testing and for the analysis of blood biomarkers (mandatory for participants with body weight ≥30 kg and optional for participants with body weight ≥15 kg and <30 kg). All assessments to be performed such as vital signs, baseline assessments of urticarial symptoms, Quality of Life (QoL) indices and a complete list of study activities at screening and at the subsequent visits are provided in the flow chart (Section 1.3).

The duration of the screening period will be 2 to 4 weeks.

Treatment period:

After successful completion of the screening period, participants will begin the treatment period. All participants will be administered dupilumab subcutaneously (SC) at 1 of 4 dose regimens based on the body weight and age at the Screening visit:

- 200 mg every 4 weeks (Q4W) with no loading dose in children with body weight ≥5 kg and <15 kg.

- 300 mg Q4W with no loading dose in children with body weight ≥15 kg and <30 kg and age ≥2 to <6 years old.
- 300 mg Q4W with an initial 600 mg loading dose in children with body weight ≥15 kg and <30 kg and age ≥6 to <12 years old.
- 200 mg every 2 weeks (Q2W) with an initial 400 mg loading dose in children with body weight ≥30 kg and <60 kg.

It is recommended that participants continue their maintenance H1-antihistamine therapy, either regular or on any dosing schedule. In the setting of a CSU exacerbation, switch to another H1-antihistamine up to 4-fold the licensed dose for CSU is allowed or alternatively, a short course of oral corticosteroids (OCS) may be temporarily given at the discretion of the treating physician. Participants who permanently discontinue the study intervention will be asked and encouraged to return to the study center for all remaining study visits for follow-up.

Post-treatment period:

All participants will complete a 12-week post-treatment Follow-up period without study intervention after completing their treatment period.

Disclosure Statement: This is a single arm treatment study. There will be no masking of study drug for participants or Investigators.

Number of participants:

Depending on their body weight and age, participants will receive 1 of the 4 dose regimens of dupilumab.

The Sponsor estimates that drug concentrations in serum (primary endpoint) can be adequately assessed with approximately 24 enrolled participants with ≥8 participants in each of the 2 weight groups (≥5 kg to <30 kg and ≥30 kg to <60 kg). It is expected that a minimum of 8 participants per weight group (≥5 kg to <30 kg and ≥30 kg to <60 kg) and a total of 24 participants are sufficient and adequate to perform PK analysis.

Note: Enrolled participants are all screened participants who have been allocated to an intervention regardless of whether the intervention was received or not.

Intervention groups and duration:

Study intervention(s)

Participants who satisfy the inclusion and exclusion criteria will be assigned to 1 of the following 4 investigational medicinal product (IMP) intervention groups:

- Dupilumab:
  - 200 mg Q4W with no loading dose for participants aged ≥2 years to <12 years weighing ≥5 kg and <15 kg at Visit 2 (V2),
  - 300 mg Q4W with no loading dose for participants aged ≥2 years to <6 years weighing ≥15 kg and <30 kg at V2,

- 300 mg Q4W with an initial 600 mg loading dose in children aged ≥6 to <12 years weighing ≥15 kg and <30 kg at V2,
- 200 mg Q2W with an initial 400 mg loading dose for participants aged ≥2 years to <12 years weighing ≥30 kg and <60 kg at V2.

Investigational medicinal product

- Dupilumab 300 mg supplied in prefilled syringes.
- Dupilumab 200 mg supplied in prefilled syringes.

Dupilumab

Formulation:

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

Route of administration: SC.

Dose regimen:

The dose regimen assigned to participants will be unchanged during the study intervention period; no dose adjustment will be allowed.

- One injection of 200 mg Q4W for children aged ≥2 years to <12 years weighing ≥5 kg and <15 kg at V2 with no loading dose.
- One injection of 300 mg Q4W for children aged ≥2 years to <6 years weighing ≥15 kg and <30 kg at V2 with no loading dose.
- One injection of 300 mg Q4W after an initial loading dose of 600 mg (2 injections of 300 mg) on Day 1 for children aged ≥6 years to <12 years weighing ≥15 kg and <30 kg at V2.
- One injection of 200 mg Q2W after an initial loading dose of 400 mg (2 injections of 200 mg) on Day 1 for children aged ≥2 years to <12 years weighing ≥30 kg and <60 kg at V2.

Noninvestigational medicinal product(s)

It is recommended that participants continue their established standard of care background therapy with a long-acting non-sedating H1-antihistamines. Any dose schedule of H1-antihistamine is permissible (daily, any number of days per week) and participants do not need to be on a stable dose of H1-antihistamine prior to enrollment.

Please refer to Section 6.8.1 for rescue therapy.

Posttrial access to study medication

Not applicable.

Duration of study periods

- Screening period (2 to 4 weeks).
- Study intervention period (24 weeks ±3 days).
- Follow-up period (12 weeks ±5 days).

Statistical considerations:

- **Sample size calculations**

  Approximately 24 participants will be enrolled to study intervention with ≥8 participants in each of the 2 weight groups (≥5 kg to <30 kg and ≥30 kg to <60 kg).

  The number of participants is based on practical considerations and clinical judgment since this study is a single arm study with the primary endpoint being PK parameters. The study is not powered for hypothesis testing of efficacy endpoints.

  Based on the observed variability of PK parameters in pediatric patients with AD, it is expected that a minimum of 8 participants per weight group (≥5 kg to <30 kg and ≥30 kg to <60 kg) and a total of 24 participants is adequate to provide precision in PK parameters for CSU participants aged ≥2 years to <12 years.

- **Analysis populations**

  The analysis population for the primary PK endpoint will be the PK population which includes all exposed and treated participants with at least 1 post-baseline PK result.

  The analysis population for safety endpoints is defined as all exposed participants who took at least 1 dose of study intervention, regardless of the amount of intervention administered.

  Immunogenicity endpoints will be analyzed in the anti-drug antibody (ADA) population which includes all exposed participants treated with dupilumab with at least 1 post-baseline ADA result (positive, negative or inconclusive).

  The analysis population for the efficacy endpoints will be the intent-to-treat (ITT) population which is defined as all exposed participants.

- **Primary endpoint**

  The primary endpoint is the serum concentration of dupilumab including C_{trough} at Week 12 and Week 24. It will be summarized in the PK population using arithmetic and geometric means, standard deviation (SD), standard error of the mean (SEM), coefficient of variation (CV), minimum, median, and maximum per sampling time.

- **Main secondary endpoints**

  Incidence tables for adverse events (AEs) will be provided overall and by intervention group for all types of treatment emergent adverse events (TEAEs): all TEAEs, all treatment emergent adverse event of special interest (AESI), all treatment emergent serious adverse events (SAEs) and all TEAEs leading to permanent treatment discontinuation. The AE summaries will be generated with number (%) of participants experiencing at least 1 event.

Incidence of ADA to dupilumab over time will be calculated. ADA variables including treatment-emergent ADA will be summarized using descriptive statistics.

The continuous secondary efficacy endpoints will be analyzed and summarized using the number of observations available, mean and the corresponding 95% confidence interval (CI), SD, median, minimum, and maximum.

- **Planned database lock date**

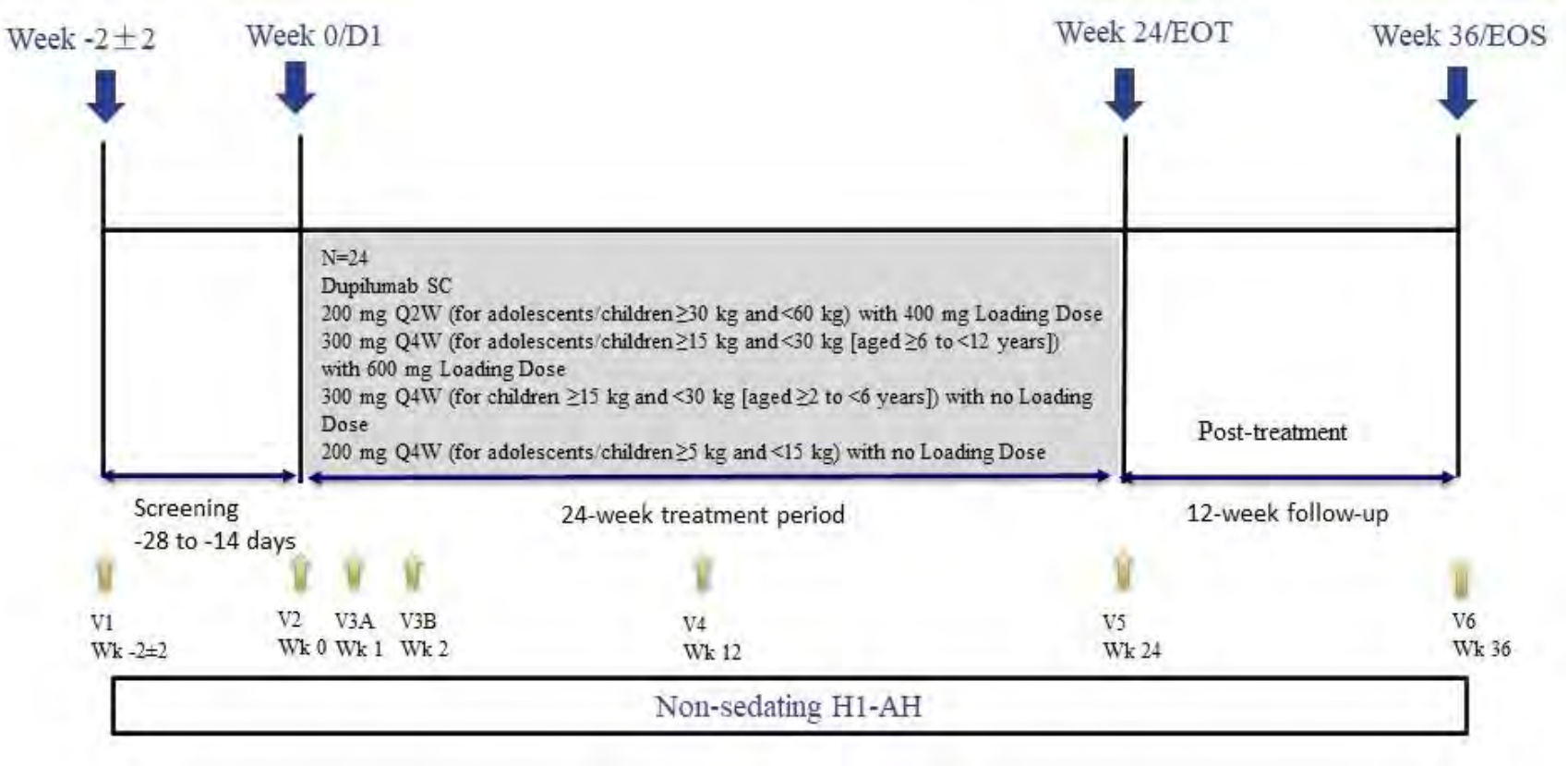
  A primary database lock will be performed when all enrolled participants have completed their treatment phase. Final analyses in the clinical study report (CSR) will be based on all data collected up to this database lock.

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

Data Monitoring/Other committee: No

1.2 SCHEMA

Figure 1 - Graphical study design



D= day; EOT= End of Treatment; EOS= End of Study; H1-AH= H1-Antihistamines; Q2W= every 2 weeks; Q4W= every 4 weeks; SC= subcutaneous; V= visit; Wk= week.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening (14 to 28 days before Day 1)	Intervention Period (24 Weeks)					Follow-up (12 weeks)
		Wk 0 (Day 1)	Wk 1	Wk 2	Wk 12	Wk 24	WK 36
Visit[a]	1	2	3A	3B	4	5 (EOT)	6 (EOS)
Screening							
Informed consent/assent[b]	X						
Inclusion and exclusion criteria[c]	X	X					
Demographics	X						
Medical history[d]	X						
Prior and concomitant medications	X	X	X	X	X	X	X
Dispense e-diary/Participant and/or parents/caregiver e-diary training[e]	X						
Study intervention							
IMP administration/ injection administration and observation training		X[f, g]					
IRT attribution treatment		X			X		
Safety[h]							
Full physical examination[i]	X	X			X	X	X
Vital signs[j]	X	X			X	X	X
12-lead ECG[k]	X					X	X
AE reporting, including SAEs	<==========X==========>						
Laboratory testing							
Hepatitis (HBsAg, HBsAb, HBcAb, HCVAb) and HIV Serology[l]	X						
Pregnancy test: *menstruating participants only*[m]	Ser	Ur			Ur	Ur	Ur
Menstruation status	X	X			X	X	X

Procedure	Screening (14 to 28 days before Day 1)	Intervention Period (24 Weeks)					Follow-up (12 weeks)
		Wk 0 (Day 1)	Wk 1	Wk 2	Wk 12	Wk 24	WK 36
Visit[a]	**1**	**2**	**3A**	**3B**	**4**	**5 (EOT)**	**6 (EOS)**
Hematology (including basophil/eosinophil counts), biochemistry, urine analysis[n,o]	X					X	
Participant's report outcome (PRO)							
Severity symptoms score questionnaires (PRO): modified UAS7, ISS7, and HSS7	X[p] Modified UAS7 (includes ISS7 and HSS7 as components), once daily from Visit 1 to Visit 6						
QoL questionnaires[q]: *C-DLQI and IDQOL*		X				X	
Pharmacokinetics and ADA[r]							
Serum PK samples for dupilumab concentration		X	X[s]	X[t]	X	X	X
Anti-dupilumab antibody		X			X	X	X
Biomarkers							
Serum Total IgE[u]		X				X	

Abbreviations: ADA = anti-drug antibodies; AEs = adverse events; AESI= adverse event of special interest; C-DLQI = Children's dermatology Life Quality Index; CRP = C-reactive protein; CSU = chronic spontaneous urticaria; ECG = electrocardiogram; eCRF = electronic case report form; E/D = early discontinuation; EOS = End of Study; EOT= End of Treatment; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibody; HIV = Human Immunodeficiency Virus; HSS7 = hive severity score over 7 days; IDQOL = Infant's dermatitis quality of life index; IgG anti-TPO = immunoglobulin G anti-thyroperoxydase; Ig E = immunoglobulin E; IMP = investigational medicinal product; ISS7 = itch severity score over 7 days; PK = pharmacokinetic; Q2W = every 2 weeks; Q4W = every 4 weeks; PRO = patient report outcome; ; rtPCR = reverse transcription–polymerase chain reaction; SAE = serious adverse event; Ser = serum; TB = tuberculosis; UAS7 = urticaria activity score over 7 days; Ur = urine.

a Allowed time window of ±3 days for each visit of treatment period and ±5 days for the Follow-up visit.

b Prior to any screening assessments: all participants ≥6 years of age (or above an age determined by the Institutional Review Board [IRB]/Independent Ethics Committee [IEC]) and their parent(s)/caregiver(s)/legal guardian(s) will receive information about the study, on study objective(s) and procedures, to the fullest extent possible, in their language and in terms they are able to understand, and must sign and date the IRB/IEC approved Informed Assent Form (IAF) and Informed Consent Form (ICF), respectively.

c The clinical status of the participant should be rechecked before first dose of study intervention.

d Medical history, allergic comorbidities history.

e Training of participants and parents/caregiver regarding completion of diary to record (a) administration of each dose of drug outside the clinic by parent/caregiver for participants; (b) completion of the assessment of participant reported questionnaires for participants aged ≥2 years to <12 years.

f 200 mg Q2W regimen of dupilumab after an initial loading dose of 400 mg on Day 1 for participants weighing ≥30 kg and <60 kg, 300 mg Q4W for participants aged ≥2 years to <6 years weighing ≥15 kg and <30 kg with no loading dose, 300 mg Q4W after an initial loading dose of 600 mg on Day 1 for participants aged ≥6 years to <12 years weighing ≥15 kg and <30 kg, and 200 mg Q4W with no loading dose for participants weighing ≥5 kg and <15 kg at Day 1. The planned last dose will be at Week 22 for Q2W injections and Week 20 for QW4 injections.

g Regardless of the participant's age, IMP administration may be performed either at study clinic visits, or by a visiting home nurse or by participant (if ≥12 years of age)/participants' parent(s)/caregiver(s)/legally authorized representative trained by the Investigator or designee on how to prepare and administer IMP and how to observe the participant after injection. The injection and observation training will be applicable to the participant (if ≥12 years of age)/parent(s)/caregiver(s)/legally authorized representative of participants who wish to administer IMP at home. This training will be performed at Day 1 and may also take place later at any visit in the study if participant (if ≥12 years of age)/parent(s)/caregiver(s)/legally authorized representative wish to change to do home injection after initially not choosing this. This training must be documented in the participant's study file. In the cases where the participant (if ≥12 years of age)/participants' parent(s)/caregiver(s) prefer not to do home injections, home nurse visits may be arranged to administer the IMP according to the planned dose schedule.

h Assessments/procedures should be conducted in the following order: patient-reported outcomes, Investigator assessments, safety, and laboratory assessments (including sample collection for ADA, PK, biomarkers), and administration of study drug.

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

j Vital signs, including systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), temperature (°C) (same method of temperature measurement should be used during the course of the study), and respiratory rate will be measured in a semi-supine or sitting position after 5 minutes rest. Temperature and pulse rate should be measured at every on-site visit (mandatory on Week 12). Height (cm) will be measured at screening visit (V1) only. Body weight (kg) will be measured at screening visit (V1), Week 12 (V4) and at end of treatment (EOT)/End of Study (EOS) Visits.

k 12-lead electrocardiogram (ECG) after at least 10 minutes of rest in supine position (if supine is feasible for the participant). Review should be done at the study center in a timely manner to determine if there are any safety concerns and for clinical management of the participant.

l Clinical laboratory testing at screening visit (V1) will include hepatitis screen covering hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), hepatitis C virus antibodies (HCVAb), Human Immunodeficiency Virus (HIV) screen (Anti-HIV-1 and HIV-2 antibodies). In case of results showing HBsAg (negative) and HBcAb (positive), HBV DNA testing will be performed and should be confirmed negative prior to enrollment. In case of results showing HCVAb (positive), hepatitis C virus ribonucleic acid (HCV RNA) testing will be performed and should be confirmed negative prior to enrollment. Tuberculosis test will be performed locally if required and results noted in the eCRF. HBV DNA, and HIV and HCV RNA samples for confirmation purpose will only be collected if a confirmation test is requested. The collection will be done during an unscheduled visit onsite.

m Urine pregnancy testing should be done monthly in all post-menarche female participants from Visit 2 to Visit 6. If these participants prematurely discontinue the study intervention, the pregnancy testing should continue for at least 12 weeks after the last dose of study intervention. In between visits, starting after Visit 3A or 3B, urine pregnancy tests must be performed at home. For urine pregnancy test performed at home, female participants will have to complete a Home Pregnancy Test Diary. If a female participant starts menstruating during the study, the study center should be contacted in order to supply urine pregnancy dipstick for monthly testing and Home Pregnancy Test Diary.

n 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 and direct bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase. Urinalysis will include specific gravity, pH, glucose, ketones, blood, and protein. In case the urine dipstick test result is abnormal, a urine sample should be sent into the central laboratory for microscopic examination.

o Blood volume required is in accordance with "Blood sample volumes in child health research" (1). See Section 8 for additional details.

p Assessments of severity symptoms (patient report outcome, PRO) includes completion of modified UAS7 questionnaires over 7 consecutive days for CSU participants. The PRO is to be recorded in the e-diary on the same time of the day. Completion of modified UAS7 should be done by the child or parent(s)/caregiver(s)/legal guardian(s) for participants aged 4 years or older; and by parent(s)/caregiver(s) for participants aged less than 4 years.

q Quality of life will be assessed through C-DLQI questionnaires in participants ≥4 years to <12 years of age and IDQOL in participants <4 years of age.

r 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.

s For participants assigned to PK Schedule A (determined by IRT system at Visit 2): Weeks 0, 1, 12, 24, 36.

t For participants assigned to PK Schedule B (determined by IRT system at Visit 2): Weeks 0, 2, 12, 24, 36.

u Biomarker sample collection is mandatory for participants with body weight ≥ 30 kg and optional for participants with body weight ≥15 kg and <30 kg.

2 INTRODUCTION

Chronic spontaneous urticaria (CSU) is a type of chronic urticaria characterized by the appearance of itchy wheals (hives) with or without angioedema for more than 6 weeks. The symptoms occur without a specific trigger in CSU (2, 3, 4).

Chronic spontaneous urticaria (CSU) can also be referred to as chronic idiopathic urticaria (CIU) and is 1 of the most common dermatologic conditions, affecting at any time 0.5% to 1% of the population (7). In a survey conducted in 5 European countries, the prevalence of chronic urticaria and CSU in a studied pediatric population (0 to 17 years) was 1.38% (95% CI, 0.94-1.86) and 0.75% (95% CI, 0.44-1.08), respectively, and comparable to that reported in the adult population (8). The duration of the disease is generally self-limited to several years but is likely to be longer in severe cases. Chronic spontaneous urticaria has significant detrimental effects on QoL, with itch-induced sleep deprivation and psychiatric comorbidity among them. It also has a major societal impact in terms of direct and indirect health care costs as well as reduced work/school performance (7).

The pathologic mechanisms underlying CSU, while not well understood, are largely driven by mast cell activation and degranulation. Increased numbers of mast cells are found in both lesional and non-lesional skin in CSU. Activation of skin mast cells with the release of histamine and other pro-inflammatory mediators, such as IL-4 and IL-13, leads to CSU symptomatology (9). Degranulation by 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. Interleukin-4/IL-13 signaling is required for antibody isotype switching to IgE in B cells and contributes to mast cell survival (5, 6). Therefore, blockade of IL-4/IL-13 may represent a potential novel therapeutic approach for CSU patients.

The treatment guidelines for CSU are: second-generation H1-antihistamine are the first line (standard dose) and second line (high dose) therapies. Targeting IgE using the mAb omalizumab has been successful in treating CSU patients, but not all patients are responsive to this therapy. There is currently an urgent need for novel therapies to address these treatment-non-responsive patient populations.

The pathologic basis of CSU symptomatology driven by mast cell degranulation strongly suggests that novel therapies targeting signaling pathways important for mast cell survival and function may prove efficacious. Dupilumab is a human mAb directed against the IL-4Rα, which is a component of IL-4 receptors Type I and Type II, the latter being also a receptor for IL-13. The binding of dupilumab to IL-4Rα results in blockade of both IL-4 and IL-13 signaling. As a targeted immunomodulatory agent, dupilumab selectively inhibits the Type 2 immune response, which can potentially achieve the desired therapeutic effect without the side effects typically associated with the use of broad immunosuppressants. The Type 2/Th2 pathway is responsible for several pathophysiological mechanisms including mast cell and basophil degranulation. Dupilumab has shown efficacy in multiple diseases with underlying Type 2 inflammation such as AD, asthma, and CRSwNP. In these clinical studies, treatment with dupilumab resulted in continuous decreases in blood total IgE suggesting that dupilumab has an impact on mast cell function.

The objective of this study is to evaluate the effect of dupilumab on PK and safety as well as to evaluate descriptive efficacy endpoints for dupilumab in children with uncontrolled CSU aged ≥2 years to <12 years old.

2.1 STUDY RATIONALE

The prevalence of CSU is very low in the pediatric population. An analysis was conducted by the Sponsor using the electronic health record data sourced from the patients healthcare institutions in the United States (US) to estimate the incidence, prevalence and treatment patterns of CSU among the pediatric population. The prevalence was found to be 0.107% for ages 3 to 5 years, and 0.084% for ages 6 to 11 years groups.

The pathophysiologic basis of disease (see Section 2) is largely similar between adults and children. Irrespective of age, CSU is characterized by the presence of itchy wheals for more than 6 weeks with or without angioedema. Subtle differences in clinical characteristics in CSU have been observed between children and adults, for example, shorter time to remission, more frequent association with infection, and less frequent occurrence of angioedema in children (7, 10, 11). These differences do not extend to the fundamental pathophysiological underpinnings of CSU, nor do they alter the response to available treatments.

Guidelines for the treatment of CSU in infants and children are largely based on data obtained in adult studies. The international EAACI/GA2LEN/EDF/WAO guidelines have recommended a stepwise treatment approach for CSU management in pediatric patients mirroring the adult recommendations (11). Second-generation H1 antihistamines (SGH1) remain the first line of treatment for CSU for both adults and children. Pharmacological treatment should begin with a standard dose, but higher-than-normal doses of antihistamines may be required to control severe urticaria/angioedema. As many as 50% of CSU patients might not achieve satisfactory control with antihistamine therapy even when higher doses are used (12). The anti-IgE monoclonal antibody omalizumab is used as second line treatment when antihistamine dose escalation fails (13), however any use in the target age group of >2 years to <12 years in CSU patients is off-label. There remains a significant unmet need for additional therapies in the pediatric population.

The cumulative dupilumab PK data in pediatric patients with asthma and AD in different age groups further support the PK/safety study. The PK of dupilumab has been found to be consistent across disease populations (patients with CSU, AD, asthma, and CRSwNP) as well as with healthy volunteers. Thus, dose regimens in AD patients 2 to <6 years of age with exposures above the threshold for the target saturation would provide similar efficacy in this age group as in adults receiving the 300 mg Q2W regimen (with mean C_{trough} of 60.3 to 80.2 mg/L).

In patients with AD, a population PK pediatric model, incorporating data from patients 6 months to <12 years of age has been used to identify an appropriate dosing regimen in participants aged 2 to <6 years old. The proposed dosing regimen provides steady-state trough concentrations of functional dupilumab in serum similar to those observed in Phase 3 clinical studies with approved adult regimens, while maintaining maximum serum concentration observed (C_{max}) levels within the exposure range studied in adults.

In summary, the nature of the disease has not been found to influence dupilumab exposure. The dupilumab doses chosen to be investigated in pediatric patients with CSU from >2 years to <12 years old are the same than that used for other diseases and have established that PK is consistent across different dupilumab indications.

Exposure-response (E-R) relationships established in other dupilumab studies in Type 2 disease indications strongly support the proposed PK study. Exposure-response analyses of dupilumab have consistently demonstrated that pharmacologic effects reached a plateau at mean trough concentrations (C_{trough}) sufficient to saturate the target-mediated pathway that typically coincide with the saturation of the target-binding. Pediatric patients with AD (participants 6 months to <6 years, participants 6 to <12 years and adolescents) have a similar E-R relationship as adult patients with AD. Similar E-R relationships were also shown in children 6 to <12 years, adolescent, and adult patients with asthma; as well as similar E-R relationship in adolescent and adult patients with CSU. It is reasonable to assume this will also be the case for CSU patients ≥2 years to <12 years of age given that a similar trough concentration of dupilumab has been consistently associated with near maximal response across age groups within each disease population.

The selected dosing regimen for children in this study with body weight ≥5 kg and <15 kg is 200 mg Q4W with no loading dose, body weight ≥15 kg and <30 kg is 300 mg Q4W for children aged ≥2 to <6 years old with no loading dose and 300 mg Q4W with an initial loading dose of 600 mg for children aged ≥6 to <12 years old with body weight ≥15 kg and <30 kg, and for children with body weight ≥30 kg and <60 kg is initial loading dose of 400 mg followed by 200 mg Q2W. These doses are expected to achieve concentrations in serum that saturate the IL-4/IL-13 receptor in most patients, and therefore achieve the optimal benefit/risk ratio in this patient population. The ≥30 kg and <60 kg dose and the ≥15 kg and <30 kg dose regimen are harmonized with EFC16461 composed of 2 parts, Study A and Study B, in participants with CSU. Study A enrolled omalizumab-naive CSU patients aged 6 to 11 years, adolescents 12 to 17 years and adults 18 to 80 years old, with uncontrolled symptoms despite use of antihistamines while Study B enrolled adolescents aged 12 to 17 years and adults aged 18 to 80 years old who have trialed omalizumab without control of their disease. All patients received dupilumab injections for 24 weeks.

EFC16461 Study A was completed, demonstrating the efficacy of dupilumab and an acceptable safety profile in participants with CSU who remain symptomatic despite the use of H1-antihistamine treatment. Treatment with dupilumab led to a 63% reduction in itch severity compared to standard of care alone (35% reduction) as measured by a 0 to 21-point itch severity scale ($p < 0.001$). Continuous improvement to Week 24 was observed. There was also a 65% reduction in urticaria activity (itch and hives) severity with dupilumab compared to 37% with standard-of-care, as measured by a 0 to 42-point urticaria activity scale ($p<0.001$) (see Section 2.3 for additional details).

EFC16461 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.

In summary, the similar pathophysiology and treatment response in adult and pediatric patients with CSU as well as the well-established PK data and mechanism of action of dupilumab, and positive findings demonstrating the efficacy of dupilumab for CSU treatment in omalizumab naive patients, support the further evaluation of dupilumab in a PK/safety study in children ≥2 to <12 years old who have CSU.

2.2 BACKGROUND

Chronic spontaneous urticaria patients with and without angioedema experience symptoms secondary to mast cell dysregulation, which leads to significant changes affecting everyday life. Currently the standards of care include antihistamines, steroid rescue therapy and the monoclonal antibody omalizumab. There is a high unmet need for improved therapies, especially in the pediatric population.

The pathogenesis of the disease coupled with the well-established mechanism of action of dupilumab provides a strong basis for investigating the utility of using dupilumab to treat uncontrolled urticarial disease. EFC16461 (CSU) Study A which evaluated the efficacy of dupilumab in adult and adolescent participants (and also enrolled 6 to 11-year-old participants) was recently completed with positive results, meeting its primary endpoints and all of its key secondary endpoints at 24 weeks. These early data further support the rationale to target IL-4/IL-13 signaling with dupilumab in pediatric patients with CSU.

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 (See Investigator's Brochure [IB] additional details).

Recently, data for children with AD aged 6 months to 5 years showed dupilumab efficacy with an acceptable safety profile. The AE profile was similar to that seen in adults and older pediatric populations. No new safety signals specific to this age group were observed.

EFC16461 Study A was completed and demonstrated that dupilumab is efficacious versus placebo in participants with CSU who remain symptomatic despite the use of H1-antihistamine treatment (14). 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) (ISS7, range 0 to 21) at week 24, and overall urticaria activity, as measured by the key secondary composite endpoint of Urticaria Activity Score over 7 days (UAS7) (UAS7, range 0 to 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 EFC16461 Study A – ITT Population

Parameter	Placebo[a] (N=68)	Dupilumab[a] (N=70)	Differeence (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

Abbreviations: CI = confidence interval; EU = European Union; ITT = intent-to-treat; ISS7 = Itch Severity Score over 7 days; LS = Least Squares; N = number of participants; ref = referred; UAS7 = Urticaria Activity Score over 7 days; US = United States; vs = versus.

In regard to the safety endpoints, overall TEAEs 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 TEAE, whereas 54.3% of participants in the dupilumab group experienced any TEAE. Among the reported TEAEs, 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-antihistamine 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.

More detailed historical information about the known and expected benefits and risks and reasonably expected AEs of dupilumab may be found in the IB.

2.3.1 Risk assessment

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

Dupilumab has an extensive safety database including in pediatric patients aged ≥6 months to <18 years. As of 28 March 2022, 13 577 participants were enrolled into the development program for dupilumab and included in the safety population with 311 participants with urticaria. Updated data are available in the current Investigator's Brochure.

Based on information retrieved from the Margin Consolidated (MARCO) application used by the Marketing Authorisation Holder for reporting of sales data from postmarketing experience the cumulative exposure to dupilumab parenteral formulation could be estimated to be 522 786 Patient Years for the period from 01 March 2017 through 30 September 2021.

Dupilumab has been generally well tolerated in all populations tested in clinical development programs consistent with a positive benefit/risk profile. In CSU (EFC16461) Study A, all dose regimens of dupilumab used (300 mg Q2W and 200 mg Q2W) were well-tolerated with an acceptable safety profile up to 24 weeks of study intervention.

The adverse drug reactions (ADRs) identified to date for dupilumab include injection site reactions, conjunctivitis (including allergic and bacterial), oral herpes, herpes simplex (primarily mucocutaneous in nature), blepharitis, dry eye, eye pruritus, eosinophilia, serum sickness, angioedema, arthralgia, facial rash, and keratitis (including ulcerative). These ADRs were generally mild or moderate, transient, and manageable. These ADRs were not consistently observed in all indications (see IB for greater details). More significant serious allergic reactions were very rare. Importantly, no increased overall infection risk was observed in patients treated with dupilumab.

Systemic hypersensitivity is an important identified risk for dupilumab. Therapeutic proteins and monoclonal antibodies such as dupilumab are potentially immunogenic. Hypersensitivity reactions, including generalized urticaria, rash, erythema nodosum and serum sickness, serum sickness-like reactions or angioedema, were reported in less than 1% of participants who received dupilumab in clinical trials.

An important potential risk for dupilumab is "eosinophilia associated with clinical symptoms in asthma patients". The observed increase in eosinophil count is transient, which is consistent with the current understanding of the mechanism of action of dupilumab. In dupilumab asthma studies,

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

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

Other potential risks based on the safety profile in particular indications are discussed in the IB. It is anticipated that dupilumab treatment of patients with CSU will have a favorable safety profile as observed across other Type 2-driven immunological disorders.

Coronavirus Disease-2019 related risk-assessment

Currently, there are insufficient data in patients with Coronavirus Disease-2019 (COVID-19) who are being treated with dupilumab. Thus, the safety and efficacy of dupilumab in COVID-19 patients are unknown. During the course of clinical trials conducted during the COVID-19 pandemic, respiratory infections including viral infections and COVID-19 infections were monitored and these events are not listed as ADRs for dupilumab.

There are currently no clinical data available on concomitant use of dupilumab with any severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). Concomitant use of nonlive SARS-CoV-2 vaccines is not prohibited. Based on available data, no attenuation of the vaccination response is expected (15, 16).

The Sponsor also recognizes that the COVID-19 pandemic may have an impact on the conduct of clinical trials. The Sponsor will monitor the situation closely and ensure the integrity of the trial conduct and data (see Section 8).

2.3.2 Benefit assessment

Dupixent® (dupilumab) is authorized for marketing in over 60 countries/regions worldwide for the adult AD indication. Dupilumab is also authorized in multiple regions/countries for the pediatric (6 to <18 years of age) AD indication. Additionally, dupilumab is approved in multiple countries/regions for the adult and adolescent asthma indication, and in the US and European Union (EU)for pediatric patients aged 6 to 11 years with asthma. Dupilumab is also authorized in multiple countries/regions for adults with CRSwNP.

The target population of PKM16982 study are patients with CSU who remain symptomatic despite the use of H1-antihistamine treatment. These patients have failed antihistamine therapy and have uncontrolled disease. There are currently no therapies that are approved for the treatment of CSU on top of antihistamines in pediatric patients aged 2 to 11 years. Therefore, these patients have a high unmet medical need for novel effective treatment.

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/IL13 signaling is required for antibody isotype switching to IgE production in B cells and contribute to mast cell and basophil survival and function. Therefore, blockade of IL-4/IL-13 by dupilumab represents a novel therapeutic approach for CSU pediatric patients.

Participation in PKM16982 study will provide an opportunity for these patients to be treated with dupilumab that has proven efficacy in disease states (eg, AD, asthma, CRSwNP) where Type 2 inflammation is the underlying driver of the disease process, and which targets signaling pathways important for mast cell survival and function that may provide a new treatment option. It has been recently shown in EFC16461 Study A that dupilumab is effective in reducing itch and hives, improvement of urticaria control as well as QoL, in adults, adolescents and children aged 6 to 11 years old with CSU.

The patients who will participate in this study may have the potential benefit of receiving a novel treatment for an uncontrolled underlying disease process and it is anticipated that use of dupilumab will lead to reduced symptomatology associated with CSU and improved QoL for these patients.

2.3.3 Overall benefit/risk conclusion

Taking into account risk mitigation measures for study participants, the potential risks identified in association with dupilumab are justified by the anticipated benefits that may be afforded to participants with CSU.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To characterize the serum concentration of dupilumab over time	• Concentration of dupilumab in serum over time including C_{trough} at Week 12 and Week 24
Secondary	
• To assess the safety of dupilumab	• Safety and tolerability assessments: Incidence of TEAEs or SAEs
• To assess the immunogenicity of dupilumab	• Incidence of ADA to dupilumab over time
• To evaluate the improvement in health-related QoL in participants with CSU receiving dupilumab who remain symptomatic despite the use of H1-antihistamine	• Change from baseline in C-DLQI in children from 4 years to less than 12 years of age at Week 24 • Change from baseline in IDQOL in children from 2 years to less than 4 years of age at Week 24
• To assess the impact of dupilumab on urticaria activity, itch and hives severity scores in participants with CSU who remain symptomatic despite the use of H1-antihistamine	• Change from baseline in the modified UAS7[a] at Week 24 • Change from baseline in the ISS7 at Week 24 • Change from baseline in the HSS7 at Week 24

Abbreviations: ADA = antidrug antibodies; C-DLQI = Children's Dermatology Life Quality Index; CSU = chronic spontaneous urticaria; C_{trough} = trough concentration; HSS7 = hive severity score over 7 days; IDQOL= Infant's Dermatitis Quality of Life Index; ISS7 = itch severity score over 7 days; SAEs= serious adverse events; QoL= quality of life; TEAEs= treatment-emergent adverse events; UAS7 = urticaria activity score over 7 days.

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

There are no estimands for the study. All efficacy endpoints are descriptive.

3.1 APPROPRIATENESS OF MEASUREMENTS

This is a single-arm study conducted to support the CSU pediatric development programs. The target of the study is to evaluate PK and safety of children with CSU aged 2 to <12 years. Efficacy evaluations planned in the study are supportive, considering the single-arm design and low number of patients planned for inclusion.

The proposed primary endpoint is the characterization of dupilumab concentrations in serum over time, including C_{trough} at Week 12 and Week 24. The Sponsor estimates that drug concentrations in serum can be adequately assessed with approximately 24 enrolled participants treated for 24 weeks, with 5 pharmacokinetic samples taken in each participant at Week 0, 1 or 2, 12, 24 and 36. It is expected that a minimum of 8 participants per weight group~~s~~ (≥5 kg to <30 kg and ≥30 kg to <60 kg) and a total of 24 participants are sufficient and adequate to perform PK analysis.

The number of study visits and number of blood samplings are optimized to minimize burden for children. The maximum amount of blood collected from each participant per visit and per study will be compliant with “Blood sample volumes in child health research” (1). The study also allows home administration of the IMP after appropriate training of parents/caregiver/legally authorized representative is performed, or arrangements can be made for qualified study center personnel and/or health care professionals (eg, visiting nurse service) to administer IMP at participant’s home.

Safety will be evaluated as the study secondary endpoint. Planned assessments include physical examination, vital signs measurement, hematology, and biochemistry blood samplings. Blood samples will also be taken to evaluate incidence of ADA to dupilumab over time. In addition, adverse events will be collected during the study. Safety evaluations performed during the study should ensure safety of study participants and provide additional data to further support safety of dupilumab.

Chronic spontaneous urticaria patients with and without angioedema experience symptoms, mainly wheals and itching, secondary to mast cell dysregulation, which leads to significant changes affecting everyday life. The secondary efficacy assessments used in this study focus on evaluation of urticaria symptoms and participant´s QoL.

A non-validated modified urticaria activity score (mUAS) will be utilized to account for the smaller body surface area in children, such that for wheals, 0 = symptom is absent; 1 = mild: (1 to <10 wheals/24 hours); 2 = moderate: (10 to 30 wheals/24 hours); and 3 = intense: (>30 wheals/24 hours or large confluent areas of wheals). The measures of pruritis will remain unchanged from the adult scale (17). The mUAS is derived from the sum of the daily Hive Severity Score (HSS) and the daily Itch Severity Score (ISS). It will be collected daily via e-diary. Daily mUAS scores are summed over 7-day period to create the mUAS7 ranging from 0 to 42.

The validated Children’s Dermatology Life Quality Index (C-DLQI) for children aged ≥4 to <12 years and the validated Infant’s Dermatitis Quality of Life Index (IDQOL) for children aged <4 years will be used to assess QoL.

The proposed primary and secondary endpoints will address important questions related to PK and safety of dupilumab in children with CSU aged 2 to <12 years and are intended to support the pediatric development programs in CSU.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 3, multicenter, single-arm, 24-week treatment study assessing the PK and safety of dupilumab in participants ≥2 years to <12 years of age with CSU not adequately controlled with H1-antihistamine treatment.

The primary objective of this study is to characterize the PK profile and the secondary objective is to assess the safety profile of dupilumab in children aged ≥2 years to <12 years with uncontrolled CSU. This study will additionally collect clinical information regarding the response to treatment in this age group, however all efficacy analyses will be descriptive.

In this study, all enrolled participants will receive dupilumab injections in a weight/age-tiered dosing regimen for 24 weeks, followed by a 12-week post-treatment observational period at the end of the study intervention.

The study consists of 3 periods:

- Screening period (2 to 4 weeks).
- Study intervention period (24 weeks).
- Follow-up period (12 weeks).

The Sponsor estimates that drug concentrations in serum (primary endpoint) can be adequately assessed with approximately 24 enrolled participants with ≥8 participants in each of the 2 weight groups (≥5 kg to <30 kg and ≥30 kg to <60 kg). It is expected that a minimum of 8 participants per weight group~~s~~ (≥5 kg to <30 kg and ≥30 kg to <60 kg) and a total of 24 participants are sufficient and adequate to perform PK analysis.

All participants will be administered dupilumab SC at 1 of 4 dose regimens based on the body weight and age at the Screening visit:

- 200 mg Q4W with no loading dose in children with body weight ≥5 kg and <15 kg.
- 300 mg Q4W with no loading dose in children with body weight ≥15 kg and <30 kg, aged ≥2 to <6 years old.
- 300 mg Q4W with an initial 600 mg loading dose in children with body weight ≥15 kg and <30 kg, aged ≥6 to <12 years old.
- 200 mg Q2Wwith an initial 400 mg loading dose in children with body weight ≥30 kg and <60 kg.

During the treatment period, participants will continue their maintenance H1-antihistamine therapy, either regular or on any dosing schedule. In the setting of a CSU exacerbation, switch to another H1-antihistamine up to 4-fold the licensed dose for CSU is allowed or alternatively, a short course/s of OCS may be temporarily given at the discretion of the treating physician.

Participants who permanently discontinue the study intervention will be asked and encouraged to return to the study center for all remaining study visits for follow-up.

All participants will complete a 12-week post-treatment period (Follow-up period) without study intervention after completing their treatment period.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The PKM16982 study is a single-arm study designed to investigate the PK and safety of dupilumab in male and female participants ≥2 years to <12 years of age with uncontrolled CSU.

Chronic spontaneous urticaria is characterized by the intermittent appearance of itchy wheals (hives), with or without angioedema, that recur for more than 6 weeks. The activation and degranulation of tissue-resident mast cells by IgE mediated Fc epsilon receptor (FcεRI) activation and the subsequent release of inflammatory mediators, such as histamine, which leads to local tissue edema and pruritus is thought to play key roles. These pathophysiological features explain the similar treatment response of CSU patients to antihistamines and omalizumab.

The PK of dupilumab has been found to be consistent across disease populations (patients with AD, asthma, CRSwNP, EoE and CSU) as well as with healthy volunteers, and in children and adolescents with AD and asthma. Pharmacokinetics has not meaningfully varied by age once body weight is accounted for in both AD (down through age 6) and asthma (down through age 6) studies. The safety profile seen in pediatric populations has also not varied meaningfully with age.

The PK of dupilumab in patients with CSU is similar to the PK in patients with AD, asthma, and CRSwNP. Exposure-response analyses of dupilumab have consistently demonstrated that pharmacologic effects reached a plateau at mean trough concentrations (C_{trough}) sufficient to saturate the target-mediated pathway that typically coincide with the saturation of the target-binding. Pediatric patients with AD (participants 6 months to <18 years) have a similar E-R relationship as adult patients with AD. Similar E-R relationships were also shown in children 6 to <12 years, adolescent, and adult patients with asthma. It is reasonable to assume this will be the case for CSU patients ≥2 years to <12 years of age given that a similar trough concentration of dupilumab has been consistently associated with near maximal response across age groups.

The 24-week treatment duration is considered sufficient for evaluation of PK profile of dupilumab in the CSU pediatric participants and is consistent with the treatment duration studied in adults and adolescents with CSU.

It should be noted that the population PK analysis for AD patients <6 years of age indicated a longer median time to undetectable concentrations, most notably in children with body weight <15 kg than in adults; and is approximately 1.5 times longer in pediatric participants 6 to 11 years of age and 2.5 times longer in pediatric participants <6 years of age. However, considering the favorable safety profile of dupilumab, and the fact that 90% to 99% of dupilumab is washed out in these children at the end of the 12-week follow-up period, the study follow-up period duration is proposed to be consistent with other age groups. It should also be noted that based on a feasibility study it is expected to enroll about 5 participants with body weight <15kg.

To ensure safety of study participants, as per protocol, the investigator should notify the Sponsor if he/she learns of any new serious adverse events occurring after End of Study (EOS) that are considered to be reasonably related to the study intervention or participation (see Section 8.3.1). If necessary for safety monitoring, additional ADA and PK samples may be collected (See Section 8.4.1.3). Furthermore, information about the extended clearance of dupilumab will be provided in the informed consent. Parents/caregivers/legal authorized representatives will be asked to contact the study center if unexpected adverse events occur up to 24 weeks after end of the study intervention.

In summary, the similar pathophysiology and the response to treatment in adult and pediatric patients with CSU as well as the well-established PK data and mechanism of action of dupilumab support the further evaluation of dupilumab in a PK/safety study in children ≥2 to <12 years old who have CSU.

4.3 JUSTIFICATION FOR DOSE

The PK of dupilumab have been found to be consistent across populations of adult patients with AD, asthma, chronic rhinosinusitis with nasal polyposis and EoE, as well as healthy volunteers, and in children and adolescents with AD and asthma. Information on PK/PD studies is also described in the IB.

The selected dosing regimen for children in this study are:

Table 3 - Dosing Regimen in the Study

Body weight	Age	Initial dose	Subsequent dose
5 kg to <15 kg	NA	200 mg (one 200 mg injection)	200 mg Q4W
15 kg to <30 kg	≥2 to <6 years	300 mg (one 300 mg injection)	300 mg Q4W
	≥6 to <12 years	600 mg (two 300 mg injections)	300 mg Q4W
30 kg to <60 kg	NA	400 mg (two 200 mg injections)	200 mg Q2W

Abbreviations: Q2W = every 2 weeks; Q4W = every 4 weeks; NA = not applicable.

These doses are expected to achieve concentrations in serum that saturate the IL-4/IL-13 receptor and therefore achieve the optimal benefit/risk ratio in this patient population. The selected dosing regimen for children ≥2 to <12 years of age are the dose regimens used in AD pediatric patients with the same weight and age that demonstrated efficacy with a favorable safety profile. As of 28 September 2021, 918 pediatric patients with AD and 1412 pediatric and adult patients with asthma were exposed to these dosing regimens.

4.4 END OF STUDY DEFINITION

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

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

5 STUDY POPULATION

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

5.1 INCLUSION CRITERIA

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

Age

I 01. Participant must be ≥2 years to <12 years of age, at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Participants who have history of a diagnosis of CSU prior to screening (V1) or symptoms consistent with a diagnosis of CSU for at least 3 months in the Investigator's opinion.

I 03. Participants with CSU (characterized by recurrent itchy wheals with or without angioedema for >6 weeks) who remain symptomatic at the time of screening despite regular H1-antihistamine treatment.

I 04. This criterion is deleted as per amendment 01.

I 05. This criterion is deleted as per amendment 01.

Weight

I 06. Body weight within ≥5 kg to <60 kg.

Sex, contraceptive/barrier method and pregnancy testing requirements/breastfeeding

I 07. Female

- Contraceptive use by female participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
- 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) as defined in Appendix 4 (Section 10.4),

    OR
  - Is post-menarche and agrees to use a contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix 4 (Section 10.4) during the intervention period and for at least 12 weeks after the last dose of study intervention.

A post-menarche female participant must have a negative highly sensitive (Appendix 2 [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 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 post-menarche female participant with an early undetected pregnancy.

Informed Consent

I 08. Participant's legally authorized representative capable of giving signed informed consent as described in Appendix 1 of the protocol (see Section 10.1.3) which includes compliance with the requirements and restrictions listed in the ICF and in this protocol. Participants ≥6 years of age to <12 years of age as determined by the IRB/IEC and in accordance with the local regulations and requirements must provide written informed assent, and the participant's legally authorized representative must provide written informed consent (Appendix 1 of the protocol, see Section 10.1.3).

I 09. Participant/parent(s)/caregiver(s)/participant's legally authorized representative, as appropriate, willing and able to comply with study visits and related procedures.

I 10. Participant/parent(s)/caregiver(s)/participant's legally authorized representative, as appropriate, must be able to understand and complete study-related questionnaires.

5.2 EXCLUSION CRITERIA

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

Medical conditions

E 01. Underlying etiology for chronic urticarias other than CSU. This includes, but is not limited to the following conditions:

- Inducible urticaria: acute urticaria, solar, cholinergic, heat, aquagenic, vibratory angioedema, symptomatic dermographism, delayed pressure, or contact.
- Diseases with possible symptoms of urticaria or angioedema: hereditary alpha tryptasemia, systemic lupus erythematosus, urticarial vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, hereditary or acquired angioedema, lymphoma, leukemia, or generalized cancer.

E 02. Presence of skin morbidities other than CSU that may interfere with the assessment of the study outcomes.

E 03. Participants with a concurrent diagnosis of chronic inducible cold urticaria.

E 04. Participants 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), autoimmune diseases (eg, lupus, inflammatory bowel disease, rheumatoid arthritis, etc), other severe endocrinological, gastrointestinal, metabolic, pulmonary, psychiatric, or lymphatic diseases. The specific justification for participants excluded under this criterion will be noted in study documents (chart notes, electronic case report forms [eCRF], etc).

E 06. Participants 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, or if TB is suspected by the investigator.

E 07. Diagnosed with, suspected of, or at high risk of endoparasitic infection, and/or use of antiparasitic drug within 2 weeks before the screening visit (V1) or during the screening period.

E 08. History of human immunodeficiency virus (HIV) infection or positive HIV 1/2 serology at the screening visit (V1).

E 09. Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, or antifungals within 2 weeks before the screening visit (V1) or during the screening period.

E 10. Known or suspected immunodeficiency, including history of invasive opportunistic infections (eg, 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 11. Active malignancy or history of malignancy within 5 years before the baseline visit.

E 12. History of systemic hypersensitivity or anaphylaxis to dupilumab including any excipient.

E 13. Known or suspected alcohol and/or drug abuse.

E 14. Participant 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 participant's participation unreliable, or may interfere with study assessments. The specific justification for participants excluded under this criterion will be noted in study documents (chart notes, eCRF, etc).

Prior/concomitant therapy

E 15. Planned or anticipated major surgical procedure during the participant's participation in this study.

E 16. Participant who has taken biologic therapy (disease modifiers)/systemic immunosuppressant/immunomodulator within 4 weeks before the screening visit (V1) or 5 half-lives, whichever is longer.

E 17. Prior use of omalizumab.

E 18. Treatment with a live (attenuated) vaccine within 4 weeks before the screening visit (V1).

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

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

E 19. Either intravenous immunoglobulin (IVIG) therapy and/or plasmapheresis within 4 weeks before the screening visit (V1).

E 20. Use of any prohibited medications (Section 6.8) and procedures during screening period or planned use during screening or study treatment period.

Prior/concurrent clinical study experience

E 21. Current participation to any clinical trial of an investigational drug or device or participation within 3 months before the screening visit or 5 half-lives of the investigational compound, whichever is longer.

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

Diagnostic assessments

E 23. Participants with any of the following result at the screening visit (V1):

- Positive (or indeterminate) hepatitis B surface antigen or,
- Positive total hepatitis B core antibody confirmed by positive hepatitis B virus DNA or,
- Positive hepatitis C virus antibodies (HCVAb) confirmed by positive hepatitis C virus ribonucleic acid (HCV RNA).

Noncompliance to completion of the e-diary

E 24. Participants are not complaint with completion of e-diary by completing entries on less than 4 days out of 7 days immediately preceding the baseline visit (Visit 2).

Other exclusions

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

E 26. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 27. Participant's legally authorized representative(s) are employees of the clinical study center or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with Section 1.61 of the ICH-GCP Ordinance E6).

E 28. 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.

E 29. Any country-related specific regulation that would prevent the participant from entering the study - see Appendix 7 of the protocol (Section 10.7) (country-specific requirements).

5.3 LIFESTYLE CONSIDERATIONS

Not Applicable.

5.4 SCREEN FAILURES

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently enrolled. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any SAE.

In cases where the original screen failure was due to reasons expected to change at rescreening and based upon the Investigator's clinical judgment, the participant can be rescreened 1 time for this study.

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

During a regional or national emergency declared by a governmental agency, if the study center is unable to adequately follow protocol mandated procedures, contingency measures are proposed in Appendix 8 (Section 10.8): Contingency measures for a regional or national emergency that is declared by a governmental agency and should be considered for screening/enrollment/administration of study intervention.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 4 - Study intervention(s) administered

Intervention label	Dupilumab 200 mg	Dupilumab 300 mg
Intervention name	Dupilumab 200 mg	Dupilumab 300 mg
Intervention description	Solution for injection	Solution for injection
Type	Biological/Vaccine	Biological/Vaccine
Dose formulation	Dupilumab 200 mg: a 175 mg/mL dupilumab solution in a prefilled syringe to deliver 200 mg in 1.14 mL	Dupilumab 300 mg: a 150 mg/mL dupilumab solution in a prefilled syringe to deliver 300 mg in 2 mL
Unit dose strength(s)	200 mg	300 mg
Dosage level(s)	200 mg every 14 ±3 days after an initial loading dose of 400 mg Or 200 mg every 28 ±3 days	≥6 to <12 years of age: 300 mg every 28 ±3 days after an initial loading dose of 600 mg Or ≥2 to <6 years of age: 300 mg every 28 ±3 days
Route of administration	SC injection[a]	SC injection[a]
Use	Experimental	Experimental
IMP and NIMP	IMP	IMP
Packaging and labeling	One glass prefilled syringe packed in a patient kit box. Both glass prefilled syringe and box will be labeled as required per country requirement.	One glass prefilled syringe packed in a patient kit box. Both glass prefilled syringe and box will be labeled as required per country requirement.
[Current/former name(s) or alias(es)]	Dupixent	Dupixent

a 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(s)/caregiver(s)/legally authorized representative) trained by Investigator or Delegate or health care professional but not the participants themselves.

Table 5 - Study arm

Arm title	Dupilumab
Arm type	Experimental
Arm description	200 mg every 14±3 days after an initial loading dose of 400mg Or 200 mg every 28±3 days Or 300 mg every 28±3 days after an initial loading dose of 600 mg for children aged ≥6 to 12< years. Or 300 mg every 28±3 days for children aged ≥2 to <6 years old
Associated intervention labels	Dupilumab 200 mg Dupilumab 300 mg

The first IMP administration should be performed at the study center. Subsequent IMP administrations can be done at home by the participant (if ≥12 years of age)/parent/legally authorized representative, or caregiver. The Investigator or delegate will train the participant (if ≥12 years of age)/parent(s)/legally authorized representative/caregiver how to prepare and inject IMP at Day 1 and may also take place later at any visit in the study if the participant (if ≥12 years of age)/parent(s)/caregiver(s)/legally authorized representative wish to change to do home injections after initially not choosing this. The Investigator or delegate will prepare and inject a dose of IMP in front of the participant (if ≥12 years of age)/participants' parent(s)/legally authorized representative/caregiver(s). The participant (if ≥12 years of age)/participants' parent(s)/legally authorized representative/caregiver(s) will prepare and inject the IMP under the supervision of the Investigator or delegate. This training must be documented in the participant's study file and in the Patient User Instruction Manual. In case of emergency (eg, natural disaster, pandemic, etc.) different training ways (eg, training remotely with instruction provided by phone, etc) can be performed (and will be documented in the participant's study file).

Note: Participants <12 years of age are not permitted to perform any IMP self-administration. Participants ≥12 to <18 years of age, if trained, are permitted to perform IMP self-administration at home (except for injections in the upper arms) under the supervision of their trained parents/ legally authorized representatives/caregivers.

If the participant (if ≥12 years of age)/parent/legally authorized representative or trained caregiver is unable or unwilling to prepare and inject IMP, injections can be performed at the study center by way of unscheduled visits; or arrangements can be made for qualified study center personnel and/or health care professionals (eg, visiting nurse service) to administer IMP at participant's home.

A Parent/legally authorized representative, or caregiver should also be trained by the study center staff to recognize potential signs and symptoms of hypersensitivity reaction in order to monitor children at home for at least 30 minutes (or longer per country specific or local study center-specific requirements) following injection. In case of hypersensitivity symptoms, the parent/legally authorized representative, or caregiver should contact healthcare provider/emergency. The training must be documented in the participant's study file.

When the participant has a study visit, the IMP will be administered following clinical procedures and blood collection. Participants should be monitored for at least 30 minutes. The monitoring period may be extended as per country specific or local study center-specific requirements.

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. The IMP injection should be avoided in areas where participants have urticaria or angioedema.

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

The dupilumab 200 mg and 300 mg may be supplied at the study center or from the Investigator/study center/Sponsor to the participant via a Sponsor-approved courier company when allowed by local regulations and agreed upon by the participant.

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted study center access, contingency measures are included in Appendix 8 (Section 10.8): Contingency measures for a regional or national emergency that is declared by a governmental agency.

6.1.1 Noninvestigational medicinal products

It is recommended that participants continue their established standard of care background therapy with a long-acting non-sedating H1-antihistamines (for Japan please see Appendix 7 Section 10.7). In the setting of a CSU exacerbation, switch to another H1-antihistamine up to 4-fold the licensed dose for the CSU is allowed or alternatively, a short course/s of OCS may be temporarily given at the discretion of the treating physician. Any dose schedule of H1-antihistamine is permissible (daily, any number of days per week) and participants do not need to be on a stable dose of H1-antihistamine prior to enrollment.

Any change to H1-antihistamine therapy should be documented in the eCRF including the date of change as well as the dosage regimen.

Please refer to Section 6.8.1 for rescue therapy.

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

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

6.1.2 Devices

Not applicable.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions 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 study center 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 study center 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).

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

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

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

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is a single-arm study. Randomization and blinding is not applicable.

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

Approximately 24 participants will be enrolled in the study with ≥ 8 participants in each of the 2 weight groups (≥5 kg to <30 kg and ≥30 kg to <60 kg). It is expected that a minimum of 8 participants per weight group~~s~~ (≥5 kg to <30 kg and ≥30 kg to <60 kg) and a total of 24 participants are sufficient and adequate to perform PK analysis.

If a participant who had previously failed screening is approached for rescreening, a new ICF must be signed. In such case, a new participant number will be assigned by IRT.

A participant cannot be enrolled more than once in the study. Study intervention will be dispensed at the study visits summarized in schedule of activities (SoA) (Section 1.3). Returned study intervention should not be re-dispensed to the participants.

6.4 STUDY INTERVENTION COMPLIANCE

IMP compliance:

- Intervention units are returned by the participant at each visit. In case of DTP process, the intervention units can be returned by the carrier (if defined in the contract).
- The Investigator or his/her delegate counts the number of remaining kits/prefilled syringes and completes in the intervention log form and inventory.
- The Investigator records the dosing information on the appropriate page(s) of the eCRF.
- The monitor in charge of the study then checks the eCRF data by comparing them with the IMP which he/she has retrieved and intervention log forms.

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

When the parent(s)/caregiver(s)/legal authorized representative administers the injection to participant at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned prefilled syringes, etc, during the study center visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of prefilled syringes dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

6.5 DOSE MODIFICATION

No change in IMP dose is allowed.

6.6 CONTINUED ACCESS TO 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.

6.7 TREATMENT OF OVERDOSE

For this study, any dose of IMP greater than twice the intended dose during an interval of less than 11 (for Q2W)/25 (for Q4W) days will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

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

1. Closely monitor the participant for any AE/SAE and laboratory abnormalities until dupilumab can no longer be detected systemically (at least 98 days).
2. Evaluate the participant to determine, in consultation with the Sponsor, whether study intervention should be interrupted.
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 Sponsor (determined on a case-by-case basis).
4. Document appropriately in the eCRF.
5. Contact the Sponsor immediately.

6.8 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, 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:

- Name of the medication (International Nonproprietary Name, [INN]).
- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

The Sponsor should be contacted if there are any questions regarding concomitant or prior therapy.

Long-acting, non-sedating H1-antihistamine, at up to 4-fold the licensed dose for CSU, are allowed as background medication and on demand as recue medication (for participants in Japan, please see Appendix 7 [Section 10.7]).

The concomitant use of the following therapies is prohibited during the entire study:

- Live vaccine (the study treatment should be permanently discontinued if live vaccine is administered).
- Systemic immunosuppressants (immunosuppressive/immunomodulating drugs) eg, systemic corticosteroids (oral or parenteral [intravenous, intramuscular, SC]), cyclosporine, mycophenolate-mofetil, interferon gamma, azathioprine, methotrexate, hydroxychloroquine, dapsone, sulfasalazine, colchicine, etc.

Note: short courses of OCS are allowed as rescue therapy (see Section 6.8.1).

- Other monoclonal antibodies (which are biological response modifiers).
- Any cell-depleting agents within 6 months of screening visit.
- IVIG.
- Plasmapheresis.
- Other investigational drugs.

6.8.1 Rescue medicine

All participants will be allowed to increase the dose of their background H1-antihistamine (Section 6.1.1) as rescue therapy as long as they do not exceed 4-fold the licensed dose for CSU during the treatment and follow-up periods. If symptoms are still uncontrolled after increase of H1-antihistamine to the maximum allowed dose, or if the participant is already on the 4-fold H1-antihistamine, participants can switch to another H1-antihistamine up to 4-fold the licensed dose for CSU or alternatively, a short course of OCS is allowed during the treatment and follow-up periods.

In order to ensure consistency, when possible, it is recommended to use OCS for 5 to 7 days followed by a taper per the Investigator's judgment.

For rescue medication in participants in Japan, please see Appendix 7 (Section 10.7).

The participants should continue their maintenance dose of H1-antihistamine once rescue treatment is no longer required.

For other information related to H1-antihistamine and OCS including safety precautions please refer to the National Product labeling. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication should be documented in the eCRF.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific study centers or of the study as a whole are detailed in Appendix 1 (Section 10.1).

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Permanent discontinuation

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety.

The participants or their parent(s)/caregiver(s)/legally authorized representative may withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or by 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 parent(s)/caregiver(s)/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
- Pregnancy (Section 8.3.5).
- Anaphylactic reactions or systemic hypersensitivity reactions that are related to IMP and require treatment (Section 10.9).
- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin.
- Any opportunistic infection or other infections whose nature or course may suggest an immunocompromised status (see Section 10.10 for the list)
- 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); baseline is defined as the latest value before the first IMP administration.
- Administration of a live vaccine (see Section 6.8 and Section 10.11).

Any abnormal laboratory value or electrocardiogram (ECG) parameter will be immediately rechecked for confirmation within a reasonable timeframe as assessed by the Investigator before deciding to permanently discontinue the IMP for the concerned participant.

Handling of participants after permanent 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.

If possible, and after the permanent discontinuation of intervention, the participants will be assessed using the procedure normally planned for the end of treatment (EOT) visit, 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 participants 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. Under exceptional circumstances when a participant cannot come to the study center for a scheduled visit, a phone contact can be made.

During the phone contact, at a minimum information about AEs, concomitant medication, and status of chronic urticaria should be collected (See also Section 7.2).

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

7.1.2 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Appendix 8 [Section 10.8]: Contingency measures for a regional or national emergency that is declared by a governmental agency).

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 the infection resolves.

Following a temporary interruption or missed dose, the treatment should be reinitiated at the next scheduled administration, maintaining the planned dose.

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

7.1.3 Rechallenge

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

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 8 (Section 10.8): Contingency measures for a regional or national emergency that is declared by a governmental agency.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at the request of parent(s)/caregiver(s)/legally authorized representative or his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See 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.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study center records.

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

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

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

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

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

Participants who have withdrawn from the study cannot be retreated 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 center.

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

- The study center must attempt to contact the participant/parent(s)/caregiver(s)/legally authorized representative and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether 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.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, 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, urine tests) 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 timeframe defined in the SoA (Section 1.3).
- The maximum amount of blood collected from each participant will be compliant with "Blood sample volumes in child health research" (1) which specifies that pediatric blood sample volume should not exceed 1% to 5% of total blood volume (TBV) over 24 hours and up to 10% of TBV over 8 weeks. Overall, the maximum amount of blood collected from each participant with body weight < 15 kg, ≥ 15 kg and <30 kg, and ≥ 30 kg over the duration of the study, will not exceed approximately 18 mL, 22 mL, and 31mL, respectively. The amount of blood collected from each participant at study visit depends on type of sampling and participant's body weight, and ranges from approximately 1.2 mL to 11 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- It is recommended that assessments/procedures at a study center visit are performed in the following order if possible:
  - Patient-reported outcomes (C-DLQI/IDLQI),
  - Safety and laboratory assessments (including sample collection for PK, ADA, and biomarkers [mandatory for participants with body weight ≥30 kg and optional for participants with body weight ≥15 kg and <30 kg]),
  - Administration of IMP.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 8 (Section 10.8): Contingency measures for a regional or national emergency that is declared by a governmental agency.

8.1 EFFICACY ASSESSMENTS

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.3).

The e-diary is used for daily recording of modified UAS7 and for assessment of C-DLQI (≥4 to <16 years old) and IDQOL (<4 years old) during study center visits.

8.1.1 Children's Dermatology Quality Life Quality Index (to be completed for all participants)

The C-DLQI is a validated questionnaire designed to measure the impact of skin disease on children's Health-Related Quality of Life (HRQoL) HRQoL (18). The questionnaire is validated for children aged ≥4 to <16 years. The C-DLQI is recommended for children aged 4 to 12, participants should complete the questionnaire themselves, however, younger children may complete the questionnaire with assistance from their parent/caregiver. 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 1week (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 C-DLQI 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.

8.1.2 Infants' Dermatitis Quality of Life Index (to be completed for all participants)

The IDQOL (19) is a validated questionnaire designed for use in children aged <4 years. The questionnaire is completed by the child's caregiver/guardian. The instrument has a recall period of 1 week (7 days). There are 11 questions in total, 10 focusing on the topic of Life Quality Index scored on a 4-point Likert Scale plus an additional question scored on a 5-point Likert Scale focusing on Dermatitis Severity. For the Life Quality Index, questions 1, 5 - 10, the scoring is: All the time = 3 to None = 0. For question 2, the scoring is: Always crying, etc = 3, Very fretful = 2, Slightly fretful = 1, Happy = 0. For question 3, the scoring is: More than 2 hours = 3, 1 to 2 hours = 2, 15 minutes to 1 hour = 1, 0 to15 minutes = 0. For question 4, the scoring is: 5 hours or more = 3, 3 to 4 hours = 2, 1 to 2 hours = 1, Less than 1 hour = 0. For the Dermatitis Severity, the 5-point Likert Scale scoring is: Extremely severe = 4 to None = 0. The IDQOL 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.

8.1.3 Modified Urticaria Activity Score

The Urticaria Activity Score (UAS) is a validated patient reported outcome (PRO) measure. A modified version of the UAS (mUAS) will be used in this study to account for the smaller body surface area of child and adolescent patients. The mUAS is derived from the sum of the daily HSS (ranging from 0 to 3 [0 = absent, 1 = mild:{1 to <10 wheals/24 hours}; 2 = moderate: {10 to 30 wheals/24 hours}; and 3 = intense: {>30 wheals/24 hours or large confluent areas of wheals}]) and the daily ISS (ranging from 0 = None to 3 = intense). Wheals and itching are the 2 key symptoms in urticaria. The daily mUAS total scores range from 0 to 6 (0 to 3 for the Itch Severity Score and 0 to 3 for the HSS). Daily mUAS scores are summed over 7-day period to create the UAS7, ranging from 0 to 42, and is composed of the hive severity score over 7 days (HSS7) and ISS7 components. Completion of mUAS7 should be done by the child or parent(s)/caregiver(s)/legal guardian(s) for participants aged 4 years or older; and by parent(s)/caregiver(s) for participants aged less than 4 years.

The UAS7 (20) is an established and widely accepted PRO tool to prospectively measure CSU activity. A minimal important difference (MID) (21, 22, 23) value ranging from 9.5 to 10.5 has been defined to help interpretation of the change in score in CSU participants.

The ISS is a single item scale scored on a 0 to 3 Likert Scale ranging from 0 = None to 3 = intense. The ISS will be collected daily and used to derive the mUAS as described above.

The HSS is a single-item scale scored on a 0 to 3 Likert Scale ranging from 0 = Absent to 3 = intense. The HSS will be collected daily and used to derive the mUAS score as described above.

8.2 SAFETY ASSESSMENTS

This section presents safety assessments other than adverse events which are presented in Section 8.3.

Planned timepoints 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.
- Height and weight will also be measured and recorded. Height and weight should be measured with indoor clothing but without shoes.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Any new finding or worsening of previous finding should be reported as a new AE.

8.2.2 Vital signs

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Same method of temperature measurement should be used during the course of the study.
- Blood pressure and pulse measurements will be assessed in a semi-supine or sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

8.2.3 Electrocardiograms

A single standard 12-lead ECG will be obtained as outlined in the SoA (Section 1.3) The ECG should be recorded after 10 minutes of rest in the supine position. The ECG will be read locally, and results reported in the eCRF. In case of a clinically significant finding the Investigator should

assess if it impacts a participant's eligibility and document this in the medical records. An AE should be reported if appropriate.

8.2.4 Clinical safety laboratory tests

- 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 significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents. Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, 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 or within 12 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.
  - If clinically significant 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 tests, 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 tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.2.5 Pregnancy testing

- Refer to Section 5.1 Inclusion criteria for pregnancy testing entry criteria; the Investigator is responsible for the review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female with an early undetected pregnancy.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted in post-menarche female participants at every month as specified in the SoA (Section 1.3).
- Pregnancy testing (urine or serum as required by local regulations) should be conducted corresponding with the time frame for female participant contraception in Section 5.1 Inclusion Criteria.
- Post-menarche female (WOCBP) participants will be supplied with urine dipsticks for use between study center visits (starting after Visit 3A or 3B) and will complete the Home Pregnancy Test Diary.

- If a female participant starts menstruating during the study, the study center should be contacted in order to supply urine pregnancy dipstick for monthly testing and Home Pregnancy Test Diary.

- Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

The definitions of AEs and SAEs can be found in Appendix 3 (Section 10.3). The definition of AESI is provided in Section 8.3.7

The definitions of unsolicited and solicited adverse events can be found in Appendix 3 (Section 10.3).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) that meet the definition of an AE or SAE and remain responsible for following up all AEs or AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention/study. (see Section 7).

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

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 follow-up visit at the timepoints specified in the SoA (Section 1.3).

All SAEs and AESI 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 data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs 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

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading 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 AEs of special interest (as defined in Section 8.3.7), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.
- Serious adverse events that are considered expected will be specified in the reference safety information (IB).
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.3.5 Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and for at least 12 weeks after the last administration of study intervention.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- 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.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

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

Signs/symptoms 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.

8.3.7 Adverse events of special interest

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

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

    Or
  - ALT >8 × ULN if baseline ALT >2 × ULN.
- Pregnancy of a female participant entered in a study with IMP:
  - Pregnancy occurring in a female participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills 1 of the seriousness criteria (see Appendix 3 [Section 10.3]),
  - In the event of pregnancy in a female participant, IMP should be discontinued,
  - Follow-up of the pregnancy in a female participant is mandatory until the outcome has been determined (See Section 8.3.5).

- Symptomatic overdose (serious or nonserious) with IMP/noninvestigational medicinal product (NIMP):
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as IMP greater than twice the intended dose during an interval of less than 11 (for Q2W)/25 (for Q4W)] days. The circumstances (ie, accidental or intentional) should be clearly specified in the eCRF,
  - An overdose (accidental or intentional) with the 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.

8.3.8 Guidelines for reporting product complaints

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

8.4 PHARMACOKINETICS

8.4.1 Systemic drug concentration and antidrug antibodies

8.4.1.1 Sampling time

Participants will be assigned by IRT system at Visit 2, 1:1, to PK schedule A (Weeks 0, 1, 12, 24, 36) or to PK schedule B (Weeks 0, 2, 12, 24, 36). Blood samples will be collected for the assessment of functional dupilumab and anti-dupilumab antibodies in serum as specified in the SoA (Section 1.3). The date of collection should be recorded in the eCRF.

8.4.1.2 Handling procedures

Special procedures for collection, storage, and shipping of serum are described in separate operational manuals.

8.4.1.3 Bioanalytic method

[redacted] Table 6.

Table 6 - [redacted]

[redacted]

8.4.2 Pharmacokinetics parameters

The PK parameters will include, but may not be limited to the following listed in Table 7.

Table 7 - List of Pharmacokinetic Parameters and definitions

C_{max}	Maximum serum concentration observed
C_{trough}	Concentration observed before treatment administration during repeated dosing
AUC_{0-t}	Area under the serum concentration versus time curve calculated using the trapezoidal method during a dose interval (τ)

8.5 GENETICS

Genetics are not evaluated in this study.

8.6 BIOMARKERS

- Whole blood will be collected to investigate exploratory markers of drug response, disease activity, safety and the Type 2 inflammation pathway. Biomarkers will include serum total IgE. Samples will be collected according to the schedule described in the SoA (Section 1.3) and as detailed in the study laboratory manual.
- Biomarker blood sampling is mandatory for participants with body weight ≥30 kg and optional for participants with body weight ≥15 kg and <30 kg.

8.7 IMMUNOGENICITY ASSESSMENTS

See Section 8.4.

8.8 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Health economics or medical resource utilization and health economics parameters are not evaluated in this study.

8.9 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

For participants who consent to the storage and use of their data and remaining (leftover) clinical samples, data and samples may be used for future research related either to the drug, the mechanism of action, and the disease or its associated conditions. Such research may include, but is not limited to, performing assessments on proteins or metabolites.

Remaining leftover samples will be used only after the study ends, ie, EOS as defined in the study protocol.

In the event future research is conducted for other purposes, the study participants/parent(s)/caregiver(s)/legally authorized representative will be informed of those purposes and will be given means to object to those research projects. Data and samples will be used in alignment with the information provided to participants in the ICF Part 2 (future research). For future research projects, all biological samples and relating data to be used will be coded such that no participant direct identifiers will be linked to them. These coded data and samples may be transferred to a Sponsor site (or a subcontractor site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

Relating data and biological samples for future research will be stored for up to 25 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.

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

9 STATISTICAL CONSIDERATIONS

The study is not powered for hypothesis testing of efficacy endpoints.

9.1 POPULATIONS FOR ANALYSES

The following populations for analyses are defined:

Table 8 - Populations for analyses

Population	Description
Screened	All participants who signed the ICF.
Enrolled	All participants from the screened population who have been allocated to an intervention regardless of whether the intervention was received or not.
Exposed	All screened participants who have taken at least 1 dose of study intervention regardless of the amount of study intervention administered.
Intent-to-treat (ITT)	All exposed participants. Participants will be analyzed according to the intervention they were allocated to.
Safety	All exposed participants who have taken at least 1 dose of study intervention, regardless of the amount of intervention administered. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic (PK)	All exposed and treated participants (safety population) with at least 1 post-baseline PK result. Participants will be analyzed according to the intervention they actually received.
ADA	All exposed participants treated with dupilumab with at least 1 post-baseline ADA result (positive, negative or inconclusive). Participants will be analyzed according to the intervention they actually received.

Participants exposed to study intervention before or without being enrolled will not be considered enrolled and will not be included in any analysis population. The safety experience of these participants will be reported separately.

Enrolled participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population.

For any participant enrolled more than once, only the data associated with the first enrollment will be used in any analysis population. The safety experience associated with any later enrollment will be reported separately.

9.2 STATISTICAL ANALYSES

The statistical analysis plan (SAP) will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.2.1 General considerations

The baseline value is defined as the last available value before the first dose of IMP. For participants enrolled but not treated, the baseline value is defined as the last available value before enrollment.

Unless otherwise specified, analyses will be performed by intervention group.

The observation period will be divided into 4 segments:

- The **pre-treatment** period is defined as the period up to first IMP administration.
- The **treatment-emergent (TE) period** is defined as the period from the first IMP administration to the last IMP administration + 98 days. The treatment-emergent period includes the following 2 periods:
  - The **on-treatment period** is defined as the period from the first IMP administration to the last administration of the IMP +14 days (+28 days for children <30 kg),
  - The **residual treatment period** is defined as the period from the end of the on-treatment period to the end of the treatment-emergent period.
- The **post-treatment period** is defined as the period from the end of the treatment-emergent period.

9.2.2 Primary endpoint(s) analyses

Serum concentrations of dupilumab including C_{trough} at Week 12 and Week 24 will be summarized in the PK population using arithmetic and geometric means, SD, SEM, CV, minimum, median, and maximum per sampling time.

9.2.3 Secondary endpoint(s) analyses

The secondary endpoints detailed in this section are TEAEs, SAEs, ADA, and efficacy endpoints.

9.2.3.1 Adverse events

General common rules for adverse events

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened, or became serious during the pre-treatment period.
- TEAEs: AEs that developed, worsened, or became serious during the treatment-emergent period.
- Post-treatment AEs: AEs that developed, worsened, or became serious during the post-treatment period.

Similarly, deaths will be analyzed in the pre-treatment, treatment-emergent and post-treatment periods.

Analysis of all adverse events

Adverse event incidence tables will be provided overall and by intervention group for all types of TEAEs: all TEAEs, all treatment emergent AESI (defined with a preferred term [PT] or a prespecified grouping), all treatment emergent SAEs and all TEAEs leading to permanent treatment discontinuation.

The AE summaries will be generated with number (%) of participants experiencing at least 1 event.

9.2.3.2 Immunogenicity analysis

The ADA analysis including neutralizing antibodies will be conducted on the ADA population. Incidence of ADA to dupilumab over time will be calculated. ADA variables including treatment-emergent ADA will be summarized using descriptive statistics.

9.2.3.3 Efficacy analysis

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

The secondary efficacy endpoints are:

- Change from baseline in C-DLQI in children from 4 years to less than 12 years of age at Week 24.
- Change from baseline in IDQOL in children from 2 years to less than 4 years of age at Week 24.
- Change from baseline in the modified UAS7 at Week 24.
- Change from baseline in the ISS7 at Week 24.
- Change from baseline in the HSS7 at Week 24.

9.2.4 Tertiary/exploratory endpoint(s) analyses

Not applicable.

9.2.5 Multiplicity adjustment

Not applicable.

9.2.6 Safety analyses

9.2.6.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

Quantitative analyses

When relevant, for laboratory variables, vital signs and ECG variables, descriptive statistics for results and changes from baseline will be provided for each planned visit window, the last value

and the worst value (minimum and/or maximum value depending on the parameter) during the on-treatment period.

Analyses according to Potentially clinically significant abnormality (PCSA)

Potentially clinically significant abnormality (PCSA) analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock.

Analyses according to PCSA will be performed based on the worst value during the treatment-emergent period, using all measurements (either local or central, either scheduled, nonscheduled, or repeated).

For laboratory variables, vital signs and ECG variables, the incidence of participants with at least 1 PCSA during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing.
- Abnormal according to PCSA criterion or criteria.

9.2.7 Other analyses

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 8 (Section 10.8): Contingency measures for a regional or national emergency that is declared by a governmental agency.

Biomarkers

Statistical analyses for biomarkers will be detailed in a separate biomarker analysis plan.

9.3 INTERIM ANALYSES

No interim analyses are planned.

A primary database lock will be performed when all enrolled 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.

9.4 SAMPLE SIZE DETERMINATION

Approximately 24 participants will be enrolled to study intervention with ≥8 participants in each of the 2 weight groups (≥5 kg to <30 kg and ≥30 kg to <60 kg).

The number of participants is based on practical considerations and clinical judgment since this study is a single arm study with the primary endpoint being based on a PK parameter. The study is not powered for hypothesis testing of efficacy endpoints.

Based on the observed variability of PK parameters in pediatric patients with AD, it is expected that a minimum of 8 participants per weight group (≥5 kg to <30 kg and ≥30 kg to <60 kg) and a total of 24 participants is adequate to provide precision in PK parameters for participants aged ≥2 years to <12 years.

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 Good Clinical Practice (GCP) guidelines,
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation – [GDPR]).
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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,
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant/parent(s)/caregiver(s)/legally authorized representative and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and,
    - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity,

- The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps,
- In case the participant has decided to opt out, the Investigator must record in the study center medical files that she/he does not want to know about such findings.

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures,
- Providing oversight of the conduct of the study at the study center and adherence to requirements of 21 Code of Federal Regulation (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (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, including the risks and benefits, to the participants/parent(s)/caregiver(s)/or their legally authorized representative and answer all questions regarding the study, including what happens to the participant when his/her participation ends.
- Participants must be informed that their participation is voluntary. Participants and parent(s)/caregiver(s)/legally authorized representative will be required to sign a statement of informed assent form and informed consent (respectively) that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the GDPR and of the French law, where applicable, and the IRB/IEC or study center. The participant assent should be obtained for all participants ≥6 years of age (or above an age determined by the IRB/IEC).
- 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.
- In case of ICF amendment while the participants are still included in the study, they must be re-consented to the most current version of the ICF(s). Where participants are not in the study anymore, teams in charge of the amendment must define if those participants must

or not re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc.).

- A copy of the ICF(s) must be provided to the participant/parent(s)/caregiver(s)/legally authorized representative, where applicable.

For participants who are rescreened, the participants and their parent(s)/caregiver(s)/legally authorized representative are required to sign a new ICF.

The ICF contains 2 separate sections that addresses the use for research of participants' data and/or samples (remaining mandatory ones). Optional exploratory research must be detailed in the section "Optional tests/procedures" and future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2. Each option is subject to an independent consent and must be confirmed by ticking a checkbox in CSICF Part 3. The Investigator or authorized designee will explain to each participant/parent(s)/caregiver(s)/legally authorized representative the objectives of the exploratory research and why data and samples are important for future research. Participants/ parent(s)/caregiver(s)/legally authorized representative 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.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 8 (Section 10.8): Contingency measures for a regional or national emergency that is declared by a governmental agency.

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy and Data Protection laws and regulations, including the GDPR. The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

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

Protection of participant data

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

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

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant/parent(s)/caregiver(s)/legally authorized representative must be informed that his/her personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant/parent(s)/caregiver(s)/legally authorized representative as described in the informed consent.
- The participant/parent(s)/caregiver(s)/legally authorized representative must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Participants/parent(s)/caregiver(s)/legally authorized representative must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation[s] details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study,
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency.

- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
  - Sanofi's Binding Corporate Rules for intra-group transfers.
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committees structure

Not applicable.

10.1.6 Dissemination of clinical study data

Study participants

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

In addition, results from clinical trials in participants 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 vivli.org.

Individual participant data and supporting clinical documents are available for request at vivli.org. 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: vivli.org.

Professionals involved in the study or in the drug development program

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

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on the 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 electronically signing the eCRF.
- Guidance on completion of eCRFs will be provided in the eCRF.
- 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, including definition of study critical data items and processes (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).
- 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 the Investigator's study file.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study center personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and study center start and closure

First act of recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first study center open and will be the study start date.

Study/Study center termination

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

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

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

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio,
  - Discontinuation of further study intervention development.
- For study center termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines,

- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator,
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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 9 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 recorded.
- 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.
- Pregnancy testing should be conducted at screening (serum), on Day 1 before the first administration of IMP (urine) and every 4 weeks (monthly) during intervention.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure corresponding with the time frame for female participant contraception in Section 5.1, Inclusion Criteria.

Table 9 - Protocol-required laboratory tests

Laboratory tests	Parameters
Hematology	
	Platelet count
	Red blood cell (RBC) count
	Hemoglobin
	Hematocrit
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Clinical chemistry[a]	
	Blood urea nitrogen (BUN)
	Creatinine
	Glucose (nonfasting)
	Lactate dehydrogenase
	Uric acid
	Total cholesterol
	Albumin
	Bicarbonate
	Creatine phosphokinase
	Potassium
	Sodium
	Chloride
	Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT)
	Alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT)
	Alkaline phosphatase[b]
	Total and direct bilirubin
	Total protein
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)
Pregnancy testing	• Serum or highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[c]

Laboratory tests	Parameters
Other screening tests	Hepatitis serologic testing at screening visit (Visit 1): hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), and hepatitis C virus antibodies (HCVAb). In case of results showing HBsAg (negative) and HBcAb (positive), an HBV DNA testing will be performed and should be confirmed negative prior to enrollment. In case of results showing HCVAb (positive), an HCV RNA testing will be performed and should be confirmed negative prior to enrollment. HBV DNA, and HIV and HCV RNA samples for confirmation purpose will only be collected if a confirmation test is requested. The collection will be done during an unscheduled visit onsite. Human Immunodeficiency Virus (HIV) serologic testing at screening visit (Visit 1): HIV screen (Anti-HIV-1 and HIV-2 antibodies).

NOTES:

a Details of increase in ALT stopping criteria and required actions and follow-up are given in Section 10.6. All events of (ALT, bilirubin, INR etc) which may indicate severe liver injury (possible Hy's Law) must be reported to Sponsor in an expedited manner (excluding studies of hepatic impairment or cirrhosis).

b If alkaline phosphatase is elevated, consider fractionating.

c 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.

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

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

Definition of unsolicited and solicited AE

- An unsolicited adverse event is an adverse event that was not solicited using a participant diary and that is communicated by a participant/participant's parent(s)/caregiver(s)/legally authorized representative who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a health care provider). The participants/participant's parent(s)/caregiver(s)/legally authorized representative will be instructed to contact the study center as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant/ participant's parent(s)/ caregiver(s)/legally authorized representative's concern. Detailed

information about reported unsolicited AEs will be collected by qualified study center personnel and documented in the participant's records.

- Unsolicited AEs that are not medically attended nor perceived as a concern by the participants/participant's parent(s)/caregiver(s)/legally authorized representative will be collected during an interview with the participants/participant's parent(s)/caregiver(s)/legally authorized representative and by review of available medical records at the next visit.
- Solicited AEs are predefined local (at the injection site) and systemic events for which the participant is specifically questioned, and which are noted by the participants in their diary.

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), eg:
  - Symptomatic and/or,
  - Requiring either corrective treatment or consultation, and/or,
  - Leading to IMP discontinuation or modification of dosing, and/or,
  - Fulfilling a seriousness criterion, and/or,
  - Defined as an AESI.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition 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 an 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 that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:

a) Results in death – includes all deaths, even those that appear to be completely unrelated to the study drug (eg, a car accident in which a patient is a passenger).

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

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

AE and SAE recording

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

the participant number, will be redacted on the copies of the medical records before submission to the Sponsor's representative.

- 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: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.
- A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- 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. 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 an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative 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 postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

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

SAE reporting to the Sponsor via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool 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 data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in the documents that will be provided during the study center initiation.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Definitions

A female is considered WOCBP (fertile) from the time of menarche.

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

10.4.2 Contraception guidance

- If locally required, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly effective methods[b] that have low user dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Highly effective methods[b] that are user dependent *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation - oral - intravaginal - transdermal - injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation - oral - injectable

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

- Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

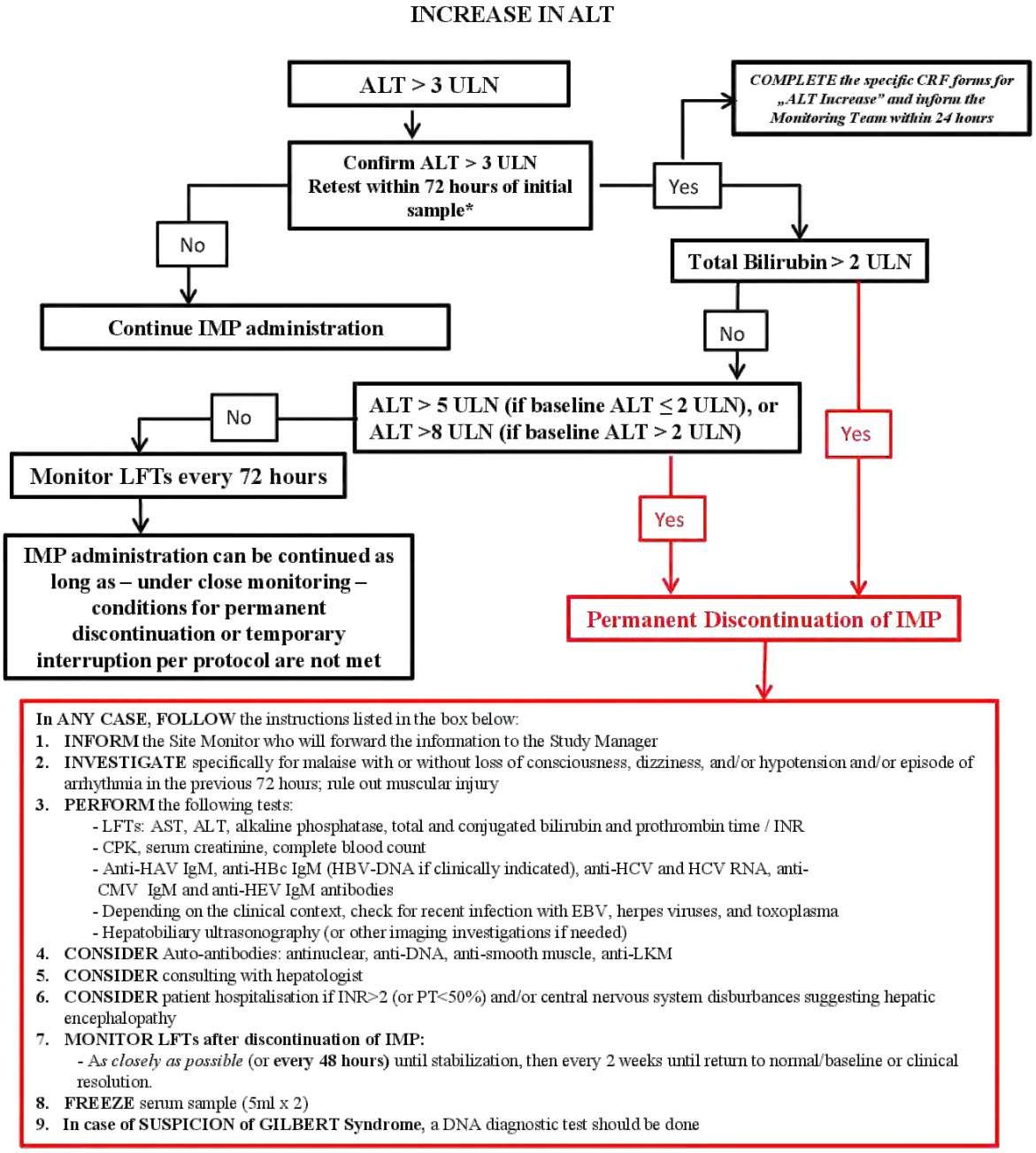
b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

10.5 APPENDIX 5: GENETICS

Not applicable.

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



*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.

10.7 APPENDIX 7: COUNTRY-SPECIFIC REQUIREMENTS

Japan

Noninvestigational medicinal products (see Section 6.1.1)

It is recommended that participants continue their established standard of care background therapy with a long-acting non-sedating H1-antihistamines up to 2-fold the licensed dose. In the setting of a CSU exacerbation, switch to another H1-antihistamine up to 2-fold the licensed dose for the CSU is allowed or alternatively, a short course/s of OCS may be temporarily given at the discretion of the treating physician. Any dose schedule of H1-antihistamine is permissible (daily, any number of days per week) and participants do not need to be on a stable dose of H1-antihistamine prior to enrollment.

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

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

Rescue medicine (see Section 6.8.1)

All participants will be allowed to increase dose of their background H1-antihistamine (Section 6.1.1) as rescue therapy as long as they do not exceed 2-fold the licensed dose for CSU during the treatment and follow-up periods. If symptoms are still uncontrolled after increase of H1-antihistamine to the maximum allowed dose, or if the participant is already on the 2-fold approved H1-antihistamine, participants can switch to another H1-antihistamine up to 2-fold the licensed dose for CSU or alternatively, a short course of OCS is allowed during the treatment and follow-up periods.

In order to ensure consistency, when possible, it is recommended to use OCS for 5 to 7 days followed by a taper per the Investigator's judgment.

The participants should continue their maintenance dose of H1-antihistamine once rescue treatment is no longer required.

For other information related to H1-antihistamine and OCS including safety precautions please refer to the National Product labeling.

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication should be documented in the eCRF.

10.8 APPENDIX 8: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

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

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

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

The decision for each individual participant to remain and/or start in the study should be made on a case by case basis based on best Investigator medical judgment. The clinical judgment of the treating physician should guide the management plan of each participant based on individual benefit/risk assessment and the evolving situation at the study center (Section 5.5). However, in case new participant eligible for the trial, the Investigator/study center should assess the capacity to maintain these patients into the trial before any screening procedures will start. If the study center cannot guarantee an accurate follow-up in the context of the trial, alternative treatment outside the clinical trial should be proposed.

When participants are already enrolled and/or treated, attempts should be made to perform all assessments in accordance with the protocol to the extent possible.

When possible, the focus should be on IMP administration and safety blood collection (eg, biochemistry and hematology). However, all efforts should be made to perform the measurements of key parameters for efficacy endpoints. The deviations from the study protocol (eg, treatment delay, omission, tests not performed) should be documented in the source document and collected in the appropriate pages of the eCRF.

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

- If onsite visits are not possible, remote visits (eg, with home nurses, home health vendor, etc.) may be planned for the collection of possible safety and/or efficacy data (eg, safety assessments, efficacy assessments, clinical outcome assessment).
- If onsite visits are not possible visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely.
- Use of local clinic or laboratory locations may be allowed.
- The DTP supply of the IMP from the study center/sponsor where allowed by local regulations and agreed upon by participant (Section 6.1).

Contingencies implemented due to emergency will be documented.

The impact of the regional or national emergency declared by a governmental agency on study conduct will be summarized (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency). Any additional analyses and methods required to evaluate the impact on efficacy (eg, missing data due to the emergency) and safety will be detailed in the SAP and in Section 9.2.7.

For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency.

The participant/parents(s)/caregiver(s)/legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension, use of local laboratory) (Section 10.1.3).

10.9 APPENDIX 9: DEFINITION OF ANAPHYLAXIS

"Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death (24)".

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.

10.10 APPENDIX 10: 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.

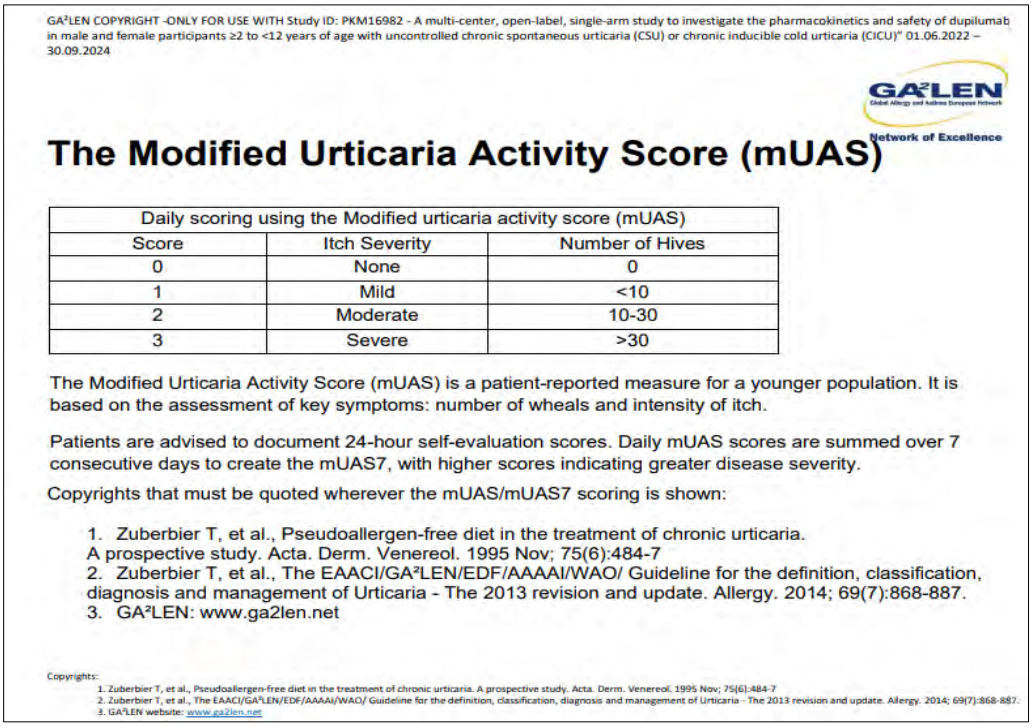
10.11 APPENDIX 11: LIST OF PROHIBITED LIVE ATTENUATED VACCINES

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

This list is indicative and not exhaustive.

10.12 APPENDIX 12: PATIENT-REPORTED OUTCOMES AND CLINICIAN-REPORTED OUTCOMES

10.12.1 Modified Urticaria Activity Score



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The Modified Urticaria Activity Score (mUAS)

Daily scoring using the Modified urticaria activity score (mUAS)		
Score	Itch Severity	Number of Hives
0	None	0
1	Mild	<10
2	Moderate	10-30
3	Severe	>30

The Modified Urticaria Activity Score (mUAS) is a patient-reported measure for a younger population. It is based on the assessment of key symptoms: number of wheals and intensity of itch.

Patients are advised to document 24-hour self-evaluation scores. Daily mUAS scores are summed over 7 consecutive days to create the mUAS7, with higher scores indicating greater disease severity.

Copyrights that must be quoted wherever the mUAS/mUAS7 scoring is shown:

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. GA²LEN: www.ga2len.net

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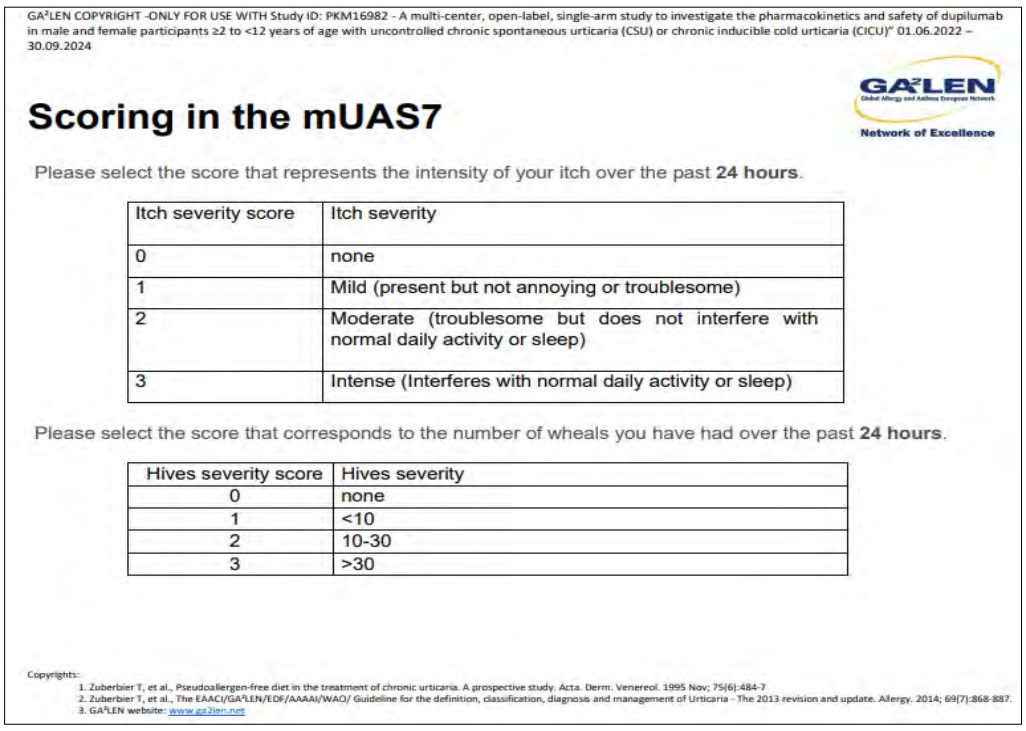
3. GA²LEN website: www.ga2len.net



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Scoring in the mUAS7

Please select the score that represents the intensity of your itch over the past **24 hours**.

Itch severity score	Itch severity
0	none
1	Mild (present but not annoying or troublesome)
2	Moderate (troublesome but does not interfere with normal daily activity or sleep)
3	Intense (Interferes with normal daily activity or sleep)

Please select the score that corresponds to the number of wheals you have had over the past **24 hours**.

Hives severity score	Hives severity
0	none
1	<10
2	10-30
3	>30

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. GA²LEN website: www.ga2len.net

Modified Urticaria Activity Score (mUAS7)

	Pruritus/Itch	Wheal/hives		
day1	3	3	=	6
day2	3	1	=	4
day3	2	1	=	3
day4	1	0	=	1
day5	3	2	=	5
day6	3	2	=	5
day7	2	1	=	3
Total	**17**	**10**	**=**	**27**

Maximum Possible Score = 42

Minimum Possible Score = 0

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.
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mUAS7 Modified Urticaria Activity Score indications over 7 days

0	Itch and hive free - indicative of no symptoms of CSU and considered a full treatment response
1–6	Well-controlled urticaria—indicates a good response to treatment
7–15	Mild urticaria - indicates also a lower response level
16–27	Moderate activity urticaria—entry criteria for clinical trials in CSU
28–42	Severe activity urticaria

- END OF UAS/UAS/mUAS/mUAS7-

Copyrights:
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10.12.2 Children´s dermatology life quality index (C-DLQI)

CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX

Hospital No
Name: Diagnosis: CDLQI SCORE:
Age:
Address: Date:

The aim of this questionnaire is to measure how much your skin problem has affected you OVER THE LAST WEEK. Please tick ✓ one box for each question.

1.	Over the last week, how **itchy**, "**scratchy**", **sore** or **painful** has your skin been?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
2.	Over the last week, how **embarrassed** or **self conscious**, **upset** or **sad** have you been because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
3.	Over the last week, how much has your skin affected your **friendships**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
4.	Over the last week, how much have you **changed** or worn **different** or **special clothes/shoes** because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
5.	Over the last week, how much has your skin trouble affected **going out**, **playing**, or **doing hobbies**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
6.	Over the last week, how much have you **avoided swimming** or **other sports** because of your skin trouble?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
7.	<u>Last week</u>, was it **school time**?	**If school time**: Over the last week, how much did your skin problem affect your **school work**?	Prevented school Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐ ☐
	OR			
	was it **holiday time**?	**If holiday time**: How much over the last week, has your skin problem interfered with your enjoyment of the **holiday**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
8.	Over the last week, how much trouble have you had because of your skin with other people **calling you names**, **teasing**, **bullying**, **asking questions** or **avoiding you**?		Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
9.	Over the last week, how much has your **sleep** been affected by your skin problem?		Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been?		Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐

Please check that you have answered EVERY question. Thank you.

10.12.3 Infants' Dermatitis Quality of Life Index (IDQOL)

Draft 7

INFANTS' DERMATITIS QUALITY OF LIFE INDEX (IDQOL)

Name: **Date:** **IDQOL SCORE** ☐
Address:

The aim of this chart is to record how your child's dermatitis has been. Each question concerns THE LAST WEEK ONLY. Please could you answer every question.

Dermatitis Severity

Over the last week, **how severe** do you think your child's dermatitis has been?; i.e. how red, scaly, inflamed or widespread.	Extremely severe	☐
	Severe	☐
	Average	☐
	Fairly good	☐
	None	☐

Life Quality Index

1.	Over the last week, how much has your child been **itching and scratching**?	All the time	☐
		A lot	☐
		A little	☐
		None	☐
2.	Over the last week, what has your child's **mood** been?	Always crying, extremely difficult	☐
		Very fretful	☐
		Slightly fretful	☐
		Happy	☐
3.	Over the last week approximately how much **time** on average has it taken **to get your child off to sleep** each night?	More than 2 hrs	☐
		1 - 2 hrs	☐
		15mins - 1 hr	☐
		0-15mins	☐
4.	Over the last week, what was the **total time** that your child's **sleep was disturbed** on average each night?	5 hrs or more	☐
		3 - 4 hrs	☐
		1 - 2 hrs	☐
		Less than 1 hour	☐
5.	Over the last week, has your child's eczema interfered with **playing or swimming**?	Very much	☐
		A lot	☐
		A little	☐
		Not at all	☐
6.	Over the last week, has your child's eczema interfered with your child **taking part in** or **enjoying other family activities**?	Very much	☐
		A lot	☐
		A little	☐
		Not at all	☐
7.	Over the last week, have there been problems with your child at **mealtimes** because of the eczema?	Very much	☐
		A lot	☐
		A little	☐
		None	☐
8.	Over the last week, have there been problems with your child caused by the **treatment**?	Very much	☐
		A lot	☐
		A little	☐
		None	☐
9.	Over the last week, has your child's eczema meant that **dressing and undressing** the child has been **uncomfortable**?	Very much	☐
		A lot	☐
		A little	☐
		None	☐
10.	Over the last week how much has your child having eczema been a problem at **bathtime**?	Very much	☐
		A lot	☐
		A little	☐
		None	☐

Please can you check that you have answered every question.

10.13 APPENDIX 13: ABBREVIATIONS

AD:	atopic dermatitis
ADA:	anti-drug antibody
ADL:	activities of daily living
ADRs:	adverse drug reactions
AEs:	adverse events
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
C-DLQI:	children's dermatology life quality index
CFR:	Code of Federal Regulation
CI:	confidence interval
Cmax:	maximum serum concentration observed
COVID-19:	coronavirus disease-2019
CRSwNP:	chronic rhinosinusitis with nasal polyposis
CSR:	clinical study report
CSU:	chronic spontaneous urticaria
CV:	coefficient of variation
DTP:	direct-to-patient
ECG:	electrocardiogram
eCRF:	electronic case report form
EOS:	end of study
EOT:	end of treatment
E-R:	exposure-response
EU:	European Union
FcεRI:	Fc gamma receptor
GDPR:	general data protection regulation
HBsAb:	hepatitis B surface antibody
HBsAg:	hepatitis B surface antigen
HCV RNA:	hepatitis C virus ribonucleic acid
HCVAb:	hepatitis C virus antibody
HIV:	human immunodeficiency virus
HRQoL:	health-related quality of life
HSS:	hive severity score
HSS7:	hive severity score over 7 days
IAF:	informed assent form
IB:	Investigator's Brochure
ICF:	informed consent form
IDQOL:	infant's dermatitis quality of life index
IEC:	Independent Ethics Committee
IgE:	immunoglobulin E
IL:	interleukin
IL-4Rα:	interleukin-4 receptor alpha
IMP:	investigational medicinal product
IRB:	Institutional Review Board

IRT:	interactive response technology
ISS:	itch severity score
ISS7:	Itch Severity Score over 7 days
ITT:	intent-to-treat
IVIG:	intravenous immunoglobulin
IVRS:	interactive voice response system
IWRS:	interactive web response system
mAb:	monoclonal antibody
mUAS:	modified urticaria activity score
NIMP:	noninvestigational product
OCS:	oral corticosteroids
PCSA:	potentially clinically significant abnormality
PK:	pharmacokinetics
PRO:	patient reported outcome
Q2W:	every 2 weeks
Q4W:	every 4 weeks
QoL:	quality of life
SAEs:	serious adverse events
SAP:	statistical analysis plan
SARS-CoV-2:	severe acute respiratory syndrome-coronavirus 2
SC:	subcutaneously
SD:	standard deviation
SEM:	standard error of the mean
SoA:	schedule of activities
SUSAR:	suspected unexpected serious adverse reaction
TB:	tuberculosis
TBV:	total blood volume
TEAEs:	treatment emergent adverse events
UAS:	urticaria activity score
UAS7:	urticaria activity score over 7 days
ULN:	upper limit of normal
US:	United States
V2:	visit 2
WOCBP:	woman of childbearing potential

10.14 APPENDIX 14: PROTOCOL AMENDMENT HISTORY

Not applicable.

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