STATISTICAL ANALYSIS PLAN

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**
Compound number (INN/Trademark):	**SAR231893 dupilumab/Dupixent®**
Study phase:	**Phase 3**
Short 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) IDKids**
Statistician:	[redacted] **(BIOTRIAL)**
Statistical project leader:	[redacted] **(Hobson Prior);** [redacted]
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VERSION HISTORY

This statistical analysis plan (SAP) for study PKM16982 is based on the amended protocol dated 31-May-2023. There are no major changes to the statistical analysis features in this SAP.

The first participant was enrolled on 08-Sep-2022.

Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1.0	04-Nov-2024	Not Applicable	Original version

1 INTRODUCTION

1.1 STUDY 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 CSU 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 and a total of 24 participants are sufficient and adequate to perform PK analysis.

All participants will be administered dupilumab subcutaneously (SC) at one of 4 dose regimens based on the body weight and age at the screening visit:

Table 1 - Dosing Regimen in the Study

Body weight	Age	Loading Dose (LD)	Dose regimen
5 kg to <15 kg	NA	NA	200 mg Q4W
15 kg to <30 kg	≥2 to <6 years	NA	300 mg Q4W
15 kg to <30 kg	≥6 to <12 years	600 mg	300 mg Q4W
30 kg to <60 kg	NA	400 mg	200 mg Q2W

LD=Loading dose; Q2W=Every 2 weeks; Q4W=Every 4 weeks; NA: Not Applicable

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

1.2 OBJECTIVES AND ENDPOINTS

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 Quality of Life (QoL) in participants with CSU receiving dupilumab who remain symptomatic despite the use of H1-antihistamine.	• Change from baseline in Children's Dermatology Life Quality Index (C-DLQI) in children from 4 years to less than 12 years of age at Week 24. • Change from baseline in Infant's Dermatitis Quality of Life Index (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 Urticaria Activity Score over 7 days (mUAS7) at Week 24. • Change from baseline in the Itch Severity Score over 7 days (ISS7) at Week 24. • Change from baseline in the Hive Severity Score over 7 days (HSS7) at Week 24.

1.2.1 Estimands

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

2 ANALYSIS POPULATIONS

The following populations for analyses are defined:

Table 3 - 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 one dose of study intervention regardless of the amount of study intervention administered.
Intent-to-treat (ITT)	All enrolled participants. Participants will be analyzed according to the intervention they were allocated to.
Population without trial impact (disruption) due to COVID-19	All enrolled participants: • without any critical or major deviation related to COVID-19, • and who did not permanently discontinue treatment due to COVID-19, • and who did not permanently discontinue the study due to COVID-19.
Safety	All enrolled participants who have taken at least one 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 enrolled and treated participants (safety population) with at least one post-baseline PK result. Participants will be analyzed according to the intervention they actually received.
ADA	All enrolled participants treated with dupilumab with at least one 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. The safety experience of these participants will be reported separately.

Enrolled participants for whom it is unclear whether they received 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.

If >10% participants are impacted by the COVID-19 pandemic, additional summaries by COVID-19 subgroups will be provided. Participants impacted by the COVID-19 pandemic are defined as enrolled participants with any critical or major deviation related to COVID-19 or who permanently discontinued study intervention or study due to COVID-19.

3 STATISTICAL ANALYSES

3.1 GENERAL CONSIDERATIONS

In general, continuous data will be summarized using the number of observations available, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum. Categorical and ordinal data will be summarized using the count and percentage of participants.

The baseline value is defined as the last available value before the first dose of IMP administration except for efficacy analysis, for which the baseline is defined in Section 3.3.1.1 and Section 3.3.1.2. For participants enrolled but not treated, the baseline value is defined as the last available value before enrollment.

Observation period

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 (+112 days for children <30 kg). 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.

Unless otherwise specified, analyses will be performed overall and by intervention group:

- 200 mg Q4W
- 300 mg Q4W
- 300 mg Q4W, 600 mg LD
- 200 mg Q2W, 400 mg LD

With the footnote: LD = Loading Dose; Q2W = Every 2 weeks; Q4W = Every 4 weeks.

3.2 PRIMARY ENDPOINT(S) ANALYSIS

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. Summary statistics may also be performed by weight or dose subgroup, if the number of participants in each subgroup allows it.

If date and/or time of the drug injection and/or sampling is missing then the concentration will not be taken into account. For treated participants and post-treatment time points, where concentration

values are below the lower limit of quantification (LLOQ), one-half of the LLOQ will be used in listings, graphic representations and summary statistics. The pre-dose concentration value at Week 0 will be used as 0 if the pre-dose concentration values at Week 0 are below the lower limit of quantitation. Values will be expressed in the tables with no more than three significant figures. All concentrations below the LLOQ and missing data will be labelled as such in the concentration data listings.

3.3 SECONDARY ENDPOINT(S) ANALYSIS

The secondary endpoints detailed in this section are efficacy endpoints.

Other secondary endpoints analyses are defined in Section 3.5.2 for AEs, and Section 3.6.1.1 for ADA analyses.

3.3.1 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).

3.3.1.1 C-DLQI and IDQOL

For participants from 4 years to less than 12 years of age:

C-DLQI items will be converted into numeric values as follows: 0=Not at all; 1=Only a little; 2=Quite a lot; 3=Very much (or "Prevented school" for item 7); for each timepoint. A global score of C-DLQI by timepoint will be computed by summing values of the 10 items.

For participants from 2 years to less than 4 years of age:

IDQOL items will be converted into numeric values for each timepoint as described in Table 4:

Table 4 - Numeric conversion for IDQOL items

Question number	Question label	Item	Numeric value of item
-	Dermatitis Severity	Extremely severe	4
		Severe	3
		Average	2
		Fairly good	1
		None	0
1	Over the last week, how much has your child been itching and scratching?	All the time	3
		A lot	2
		A little	1
		None	0

Question number	Question label	Item	Numeric value of item
2	Over the last week, what has your child's mood been?	Always crying, extremely difficult	3
		Very fretful	2
		Slightly fretful	1
		Happy	0
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 hours	3
		1 - 2 hours	2
		15mins - 1 hour	1
		0-15mins	0
4	Over the last week, what was the total time that your child's sleep was disturbed on average each night?	5 hours or more	3
		3 - 4 hours	2
		1 - 2 hours	1
		Less than 1 hour	0
5 to 10	-	Very much	3
		A lot	2
		A little	1
		Not at all/None	0

A global score of IDQOL by timepoint will be computed by summing values of the 10 life quality index items (dermatitis severity score is excluded from the calculation of the global score). Handling missing items from IDQOL will be same as for C-DLQI.

For both questionnaires, if one question is left unanswered this is scored 0 and the scores are summed and e'xpressed as usual out of a maximum of 30. If two or more questions are left unanswered the questionnaire is not scored. If two of more response options are ticked for one question, the response option with the highest score should be recorded. Baseline is considered as the closest assessment to the first IMP administration on or prior to Day 1 but no later than Day 4.

Total scores and change from baseline will be summarized quantitatively for C-DLQI and IDQOL by timepoint. Raw scores and change from baseline of dermatitis severity assessed by IDQOL questionnaire will be summarized at Week 24.

3.3.1.2 Itch and Hive Severity Scores and Modified Urticaria Activity Score

For each daily assessment:

- Itch Severity Score items will be converted into numeric values as follows: 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).

- Hive Severity Scores item will be converted into numeric values as follows:

Table 5 - Numeric values for Hives Severity Scores

Hives severity (number of hives)	Hives severity score
None	0
1-9	1
10-30	2
>30	3

The ISS7 and HSS7 baseline values are the sum of the 7 daily measurements obtained within the 7 days prior to first IMP administration. For subsequent visits, the sum of the 7 measurements on and prior to the target visit will be used (e.g., sum of days 163 through 169 for the visit at Week 24). Day ranges to be used for ISS7 and HSS7 derivations from Week 1 to Week 36 are described in Section 5.6. ISS7 and HSS7 total scores and change from baseline will be summarized quantitatively by timepoint [from baseline to End of Study (EOS)].

Handling of missing daily score: if a participant has more than 50% of non-missing daily scores within 7 days prior to the visit for baseline; and on and prior for subsequent visits, (i.e. 4 or more non-missing scores) then the weekly score will be calculated as the sum of the available scores divided by the number of non-missing daily scores and multiplied by 7. Otherwise, the weekly score will be set to missing.

Additionally, mUAS7 will be computed by summing ISS7 and HSS7 scores. mUAS7 total score and change from baseline will be summarized quantitatively by timepoint.

If one of the ISS7 or HSS7 is missing, the mUAS7 will be set to missing.

mUAS7 total score will also by summarized in category as follows by timepoint:

- 0 = Itch and hive
- 1-6 = Well-controlled urticaria
- 7-15 = Mild urticaria
- 16-27 = Moderate activity urticaria
- 28-42 = Severe activity urticaria

3.4 MULTIPLICITY ISSUES

Not applicable.

3.5 SAFETY ANALYSES

All safety analyses will be performed on the safety population as defined in Section 2, unless otherwise specified, using the following common rules:

- The analysis of the safety variables will be essentially descriptive, and no testing is planned.
- Safety data in participants who do not belong to the safety population (eg, exposed but not enrolled) will be provided.

3.5.1 Extent of exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure and compliance and summarized within the safety population. In addition, summaries will be provided by trial impact (disruption) due to COVID-19 if applicable.

Duration of IMP exposure

Duration of IMP exposure is defined as last IMP administration date – first IMP administration date +14 days (+28 days for children <30 kg), regardless of unplanned intermittent discontinuations. If the date of the last dose of IMP is missing, the duration of IMP will be left as missing.

Duration of IMP exposure (in weeks) will be summarized quantitatively and categorically:

- >0 and ≤2 weeks
- >2 and ≤4 weeks
- >4 and ≤6 weeks
- >6 and ≤8 weeks
- >8 and ≤10 weeks
- >10 and ≤12 weeks
- >12 and ≤14 weeks
- >14 and ≤16 weeks
- >16 and ≤18 weeks
- >18 and ≤20 weeks
- >20 and ≤22 weeks
- >22 and ≤24 weeks
- >24 weeks

Treatment compliance

A given administration will be considered noncompliant if the participant did not receive the number of administrations as required by the protocol.

Percentage of treatment compliance for a participant will be defined as the number of administrations that the participant was compliant divided by the total number of administrations that the participant was planned to take from the first administration of IMP up to the actual last administration of IMP.

Treatment compliance will be summarized quantitatively and categorically: <80%, ≥80%.

3.5.2 Adverse events

General common rules for adverse events

All adverse events (AEs) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version currently in effect at Sanofi at the time of database lock.

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.

The primary AE analyses will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately.

An AE with incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment or a post-treatment AE.

If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as related to IMP. Missing severity will be left as missing.

Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase.

The AE tables will be sorted as indicated in Table 6.

Table 6 - Sorting of AE tables

AE presentation	Sorting rules
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a, b]
PT	By decreasing frequency of PTs[a]

a Sorting will be based on the overall incidence
b The table of all TEAEs presented by primary SOC and PT will define the presentation order for all other tables (eg, treatment-emergent SAE) presented by SOC and PT, unless otherwise specified.

Analysis of all adverse events

Adverse event incidence tables will be provided for all types of TEAEs: all TEAEs, all treatment emergent Adverse Event of Special Interest (see Table 8), 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.

The overview of TEAE with the details below will be generated:

- Any TEAE
- Any treatment-emergent SAE
- TEAE leading to death
- Any treatment emergent AESI
- Any treatment emergent other AE grouping
- Any TEAE leading to permanent intervention discontinuation
- Any treatment-related TEAE

The AE summaries of Table 7 will be generated with number (%) of participants experiencing at least one event.

Table 7 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC and PT
TEAE related to SAR231893 as per Investigator's judgment	Primary SOC and PT
Treatment emergent SAE	Primary SOC and PT
TEAE leading to permanent study intervention discontinuation	Primary SOC and PT
Treatment emergent AESI	Primary SOC and PT
TEAE leading to death[a]	Primary SOC and PT
Pretreatment AE	Primary SOC and PT
Post-treatment AE	Primary SOC and PT

a Death as an outcome of the AE as reported by the Investigator in the AE page.

Analysis of deaths

In addition to the analyses of deaths included in Table 7 the number (%) of participants in the following categories will be provided:

- Deaths during the treatment-emergent and post-treatment periods by primary cause of death.
- Deaths in non-enrolled participants or enrolled but not treated participants.

Analysis of adverse events of special interest (AESIs) and other AEs of interest

Adverse events of special interest (AESIs) and other AEs of interest will be selected for analyses as indicated in Table 8. Number (%) of participants experiencing at least one event will be provided for each event of interest.

Table 8 - Selections for AESIs and other AEs of interest

AE Grouping	Criteria
AESI	
Anaphylactic reaction	Anaphylactic reaction algorithmic approach (Introductory Guide for Standardised MedDRA Queries (SMQs) Version 18.1): includes anaphylactic reaction narrow SMQ (20000021) terms and programmatic identification of cases based on occurrence of at least two preferred terms meeting the algorithm criteria occurring within 24 hours of each other. The latter cases identified using the algorithm will undergo blinded medical review taking into account the timing of events relative to each other and to IMP administration for final determination of an anaphylactic reaction or not.
Systemic hypersensitivity reactions	SMQ [20000214] hypersensitivity narrow search and [AE corrective treatment/therapy = 'Y' or Action taken with IMP = 'Drug withdrawn' or Action taken with IMP = 'Drug interrupted'] followed by blinded medical review (documented process) for selection of relevant systemic hypersensitivity events.
Helminthic infections	CMQ10544 based on HLGT as "Helminthic disorder".
Any severe type of conjunctivitis	CMQ10498 based on PTs (See Section 5.7)[a] and "Severe" ticked in Adverse Events eCRF page.
Any severe type of blepharitis	CMQ10497 based on HLT as "Lid, lash and lacrimal infections, irritations and inflammations" and "Severe" ticked in Adverse Events eCRF page.
Keratitis	CMQ10642 based on the following PTs [keratitis, allergic keratitis, ulcerative keratitis, atopic keratoconjunctivitis, herpes ophthalmic, ophthalmic herpes simplex, corneal infection][a].
Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)	CMQ10641 (based on HLT = Eosinophilic disorders or PT = Eosinophil count increased) and AESI is "Yes".
Pregnancy of a female patients entered in a study as well as pregnancy occurring in a female partner of a male patient entered in a study with IMP/NIMP	"Pregnancy" or "Partner Pregnancy" checked on the Pregnancy eCRF page as reported by the investigator.
Significant ALT elevation	ALT >5 × ULN in participants with baseline ALT ≤2 × ULN; OR ALT >8 × ULN if baseline ALT >2 × ULN.
Symptomatic overdose with IMP	Symptomatic Overdose is answered Yes, with Overdose of IMP answered Yes on AE eCRF.
Symptomatic overdose with NIMP	Symptomatic Overdose is answered Yes, with Overdose of NIMP answered Yes on AE eCRF.
Other selected AE Grouping	
Serious injection site reactions or severe injection site reactions that last longer than 24 hours	HLT = 'Injection site reactions' and either with serious status, or with severe status and (AE end date/time - AE start date/time) ≥24 hours or ongoing.
Severe or serious infection	Primary SOC = 'Infections and infestations' and with severe or serious status.
Drug-related hepatic disorder	SMQ [20000006] Drug-related hepatic disorders- narrow.
Injection site reaction	HLT = 'Injection site reactions'.
Malignancy	SMQ [20000091]- Malignant or unspecified tumors narrow.
Conjunctivitis (narrow)	CMQ10644 based on the following PTs [Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis][a].

AE Grouping	Criteria
Conjunctivitis (broad)	CMQ10645 based on the following PTs [Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis, Blepharitis, Dry eye, Eye irritation, Eye pruritus, Lacrimation increased, Eye discharge, Foreign body sensation in eyes, Photophobia, Xerophthalmia, Ocular hyperaemia, Conjunctival hyperaemia][a].
Conjunctivitis (FDA)	CMQ10643 based on the following PTs [Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Eye irritation, Eye inflammation, Giant papillary conjunctivitis][a].
Keratitis (FDA)	CMQ30102 based on the following PTs [keratitis, allergic keratitis, ulcerative keratitis, atopic keratoconjunctivitis, ophthalmic herpes simplex][a].

a The list of terms may be adjusted according to MedDRA version changes

3.5.3 Additional safety assessments

3.5.3.1 Laboratory variables and vital signs

The following laboratory variables and vital variables will be analyzed. They will be converted into standard international units.

- Hematology:
  - Red blood cells and platelets and coagulation: hemoglobin, hematocrit, red blood cell count, platelet count
  - White blood cells: white blood cell count, neutrophils, lymphocytes, monocytes, eosinophils, basophils
- Clinical chemistry:
  - Metabolism: glucose, total cholesterol, total protein, albumin, creatine phosphokinase
  - Electrolytes: sodium, potassium, chloride, bicarbonate
  - Renal function: creatinine, blood urea nitrogen, uric acid.
  - Liver function: alanine aminotransferase (ALT) / Serum glutamic-pyruvic transaminase (SGPT), aspartate aminotransferase (AST) / Serum glutamic-oxaloacetic transaminase (SGOT), alkaline phosphatase, lactate dehydrogenase, total and direct bilirubin
- Urinalysis:
  - Urinalysis for quantitative analysis: pH, specific gravity, proteins, glucose, blood and ketones by dipstick
- Vital signs: Temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure, weight

Data below the lower limit of quantitation/detection limit (LLOQ) will be replaced by half of the LLOQ, data above the upper limit of quantification (ULOQ) will be replaced by ULOQ value.

Quantitative analyses

When relevant, for laboratory variables and vital signs 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. For parameters for which no PCSA criteria are defined, similar analyses will be done using the normal range, if applicable.

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 and vital signs 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

3.6 OTHER ANALYSES

3.6.1 Other variables and/or parameters

3.6.1.1 Immunogenicity analyses

ADA incidence (up to the end of study) and on-treatment ADA incidence (measurements during the treatment epoch) will be provided for the following ADA response categories:

Pre-existing immunoreactivity is defined as:

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

Treatment-emergent ADA responses are defined as:

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

Treatment-emergent ADA responses are further classified as Persistent, Indeterminate or Transient

a) Persistent Response- defined as a treatment-emergent ADA response with two or more consecutive ADA positive sampling time points, separated by greater than (>) 12-week period (84 days), with no ADA negative samples in between.
b) Indeterminate Response- defined as a treatment-emergent response with only the last collected sample positive in the ADA assay
c) Transient Response - defined as a treatment-emergent response that is not considered persistent OR indeterminate

Treatment-boosted response is defined as:

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

Titer values (Titer value category)

- Low (Titer <1000)
- Moderate (1,000 ≤Titer ≤10,000)
- High (Titer >10,000)

The following summary will be provided based on ADA population:

- Number (%) of participants with pre-existing immunoreactivity
- Number (%) of participants with treatment-emergent ADA
- The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the peak post-baseline titer for participants with treatment-emergent ADA, and participants with persistent, indeterminate and transient ADA response
- Number (%) of participant with transient treatment-emergent ADA
- Number (%) of participants with persistent treatment-emergent ADA
- Number (%) of participants with indeterminate treatment-emergent ADA
- Number (%) of participants with treatment-boosted ADA
- The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the peak post-baseline titer for participants with treatment-boosted ADA
- The summary statistics (including number, mean, SD, median, Q1, Q3, minimum and maximum) of the ratio of peak post-baseline titer to baseline titer for participants with treatment-boosted ADA
- Listing of ADA peak titer levels and neutralizing antibody status
- Number (%) of participants with neutralizing antibody status

Kinetics of treatment-emergent ADA response

Number (%) of participants with treatment-emergent ADA positive response at each visit will be summarized by each intervention group.

Plot of percentage of participants with treatment-emergent ADA positive response at each visit will be provided by each intervention group.

3.6.1.1.1 Association of Immunogenicity with Exposure, Safety and Efficacy

The safety and efficacy analysis mentioned below will be conducted using the following categories:

- ADA positive participants: Participants with treatment-emergent or treatment-boosted response.
- ADA negative participants: Participants with pre-existing immunoreactivity or negative in the ADA assay at all time points.

Impact of ADA on PK profile

Potential associations between ADA variables (eg, ADA peak titers, neutralizing antibody status, treatment-emergent, persistent, indeterminate and transient response, treatment-boosted) and impact on serum concentration profile of dupilumab may be explored. Plot of serum concentration of functional dupilumab versus visit will be provided by ADA variables for each dupilumab dose group. Individual participant plots of dupilumab concentration according to ADA status will be provided.

Impact of ADA on clinical efficacy endpoints

Associations between the ADA variables (eg, ADA peak titers, neutralizing antibody status, treatment-emergent, persistent, treatment-boosted) and the efficacy endpoints may be explored.

Association of ADA with clinical safety endpoints

Association of safety versus ADA status may be analyzed in the ADA population. The safety assessment may focus on the following events:

- Severe injection site reactions last longer than 24 hours or serious injection site reactions,
- Hypersensitivity reactions (SMQ (20000214) hypersensitivity narrow search confirmed by medical review),
- Anaphylactic reactions (SMQ (20000021) anaphylactic reaction narrow search).

Associations between ADA variables (eg, ADA peak titers, neutralizing antibody status, treatment-emergent, persistent and treatment-boosted) and safety may be explored.

3.6.1.2 Quality of life analyses

Quality of life endpoints analyses are defined in Section 3.3.1.1.

3.6.1.3 Biomarker analyses

Total IgE will be summarized in the safety population. Baseline value will be the last value collected prior to the first IMP.

Descriptive statistics (including number, mean, SD, median, Q1, Q3, min, max) at baseline will be summarized and summary plots (median +/- standard error of the mean) on values at each visit, absolute changes from baseline and percent changes from baseline will be provided for the total IgE by intervention group and visit. Where values are below the lower limit of quantification

(LLOQ), one-half of the LLOQ value will always be used. Values will be expressed with two decimals.

3.6.2 Subgroup analyses

Not applicable.

3.7 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.

3.8 CHANGES TO PROTOCOL-PLANNED ANALYSES

This section summarizes major statistical changes in the protocol amendment(s).

Table 9 - Major statistical changes in protocol amendment(s)

Amendment Number	Approval Date	Changes	Rationale
Initial Version	30-Mar-2022	-	-
Protocol Amendment 01	31-May-2023	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.
		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.	These objective, endpoints and footnotes are specific to the chronic inducible cold urticaria patient group that is removed from the PKM16982 protocol.

Amendment Number	Approval Date	Changes	Rationale
		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.
		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.” 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.”	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.
		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).
		Decreased the number of PK samplings. Participants will be randomized 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.
		Added “Participants will be randomized by IRT system at randomization visit 1:1 to PK schedule A (Weeks 0, 1, 12, 24, 36) or to PK schedule B (Weeks 0, 2, 12, 24, 36)”.	
Not applicable	Not applicable	The “enrolled participants” term will be used (instead of “exposed participants”) for the definition of Intent-to-treat, population without trial impact due to COVID-19, Safety, Pharmacokinetic and ADA analysis populations.	
Not applicable	Not applicable	The definition of the TE period was updated in the SAP compared to the TE period in the protocol (addition of “(+112 days for children <30 kg)” in the definition).	

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 CSU participants aged ≥2 years to <12 years.

Enrollment was stopped after 15 participants after it was determined that drug concentration data from at least 7 participants in each weight group (≥5 kg to <30 kg and ≥30 kg to <60 kg), supplemented with PK data from pediatrics in the EFC16461 safety and efficacy studies, were considered adequate to enable the PK profile of dupilumab in children aged ≥2 years to <12 years with uncontrolled CSU to be characterized.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

AE:	adverse event
AESIs:	adverse events of special interest
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
C-DLQI:	Children's Dermatology Life Quality Index
CSU:	chronic spontaneous urticaria
EOS:	end of study
HLGT:	high-level group term
HLT:	high level term
HSS7:	hive severity score over 7 days
IDQOL:	Infant's Dermatitis Quality of Life Index
ISS7:	itch severity score over 7 days
LD:	loading dose
LLOQ:	lower limit of quantitation/detection limit
LLT:	lower-level term
MedDRA:	Medical Dictionary For Regulatory Activities
mUAS7:	modified Urticaria Activity Score over 7 days
PCSA:	potentially clinically significant abnormality
PT:	preferred term
Q2W:	every 2 weeks
Q4W:	every 4 weeks
QoL:	quality of life
SAP:	statistical analysis plan
SC:	subcutaneously
SD:	standard deviation
SOC:	system organ class
ULN:	upper limit of normal
ULOQ:	upper limit of quantification
WHO-DD:	World Health Organization-drug dictionary

5.2 APPENDIX 2 PARTICIPANT DISPOSITIONS

The number (%) of participants included in each of the analysis populations listed in Table 3 will be summarized.

Screen failures are defined as participants who consent to participate in the study but are not subsequently enrolled. The number (%) of screen failures and reasons for screen failures will be provided in the screened population.

The number (%) of participants in the following categories will be provided:

- Enrolled participants
- Enrolled but not exposed participants
- Enrolled and exposed participants
- Participants who completed the study treatment period as per protocol
- Participants who did not complete the study treatment period as per protocol and main reason for permanent intervention discontinuation
- Participants who completed the study period as per protocol
- Participants who did not complete the study period as per protocol and main reason for study discontinuation

Reasons for permanent study intervention and study discontinuation "adverse event" and "other reasons" will be split as related versus not related to COVID-19, if applicable.

The number (%) of exposed and not enrolled participants will also be summarized.

In addition, the number (%) of participants screened, screened-failed, enrolled, with permanent intervention discontinuation and with early study discontinuation will be provided by country and site.

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized in the enrolled population as well as displayed separately as related versus not related to COVID-19 if applicable.

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

Demographics, baseline characteristics, medical surgical history

The following demographics and baseline characteristics, medical and surgical history will be summarized using descriptive statistics in the exposed population.

Demographic and baseline characteristics:

- Age in years as quantitative variable and in categories (≥2 to <6 years, ≥6 to <12 years),
- Gender (Male, Female),
- Ethnic origin (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not reported, Unknown); if Asian origin (Chinese, Japanese, Asian Indian, Korean, Other, Not Reported, Unknown),
- Hispanic Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not reported, Unknown),
- Weight as quantitative variable and in categories (<15, 15 to <30, ≥30kg).

Medical and surgical history will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the MedDRA version currently in effect at Sanofi at the time of database lock. Medical and surgical history will be presented by primary SOC and PT.

Prior or concomitant medications

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the participant received prior to first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during treatment period.
- Concomitant medications are any medications received by the participant concomitantly to the IMP during the treatment-emergent period.
- Post-treatment medications are those the participant received in the period running from the end of the concomitant medications period up to the end of the study.
- A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

The prior and concomitant and post-treatment medications will be summarized for the enrolled and exposed population, by anatomic and therapeutic level. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

Analysis windows for time points

Unless stated otherwise, the following analysis windows (Table 10, Table 11, and Table 12) will decide how the post-baseline scheduled and/or unscheduled visits will be used in the by-visit analyses of efficacy, safety, biomarker and ADA variables.

A measurement (scheduled or unscheduled) will be used if it is available and measurement date is within the analysis window.

After applying these time windows, if multiple assessments are associated with the same time point, the closest from the targeted study day will be used. If the difference is a tie, the value after the targeted study day will be used. If multiple valid values exist within a same day, then the first value of the day will be selected.

If there is no measurement for a given parameter in an analysis window, data will be considered missing for the corresponding visit.

Table 10 - Analyses window definition for participants assigned to PK - Schedule A

Scheduled visit post baseline	Targeted study day	Analysis window in study days
Week 1 (Visit 3A)	8	2 to 46
Week 12 (Visit 4)	85	47 to 127
Week 24 (Visit 5 – EOT)	169	128 to 211
Week 36 (Visit 6 – EOS)	253	≥212

Study days are calculated considering Day 1 as the day of first administration of intervention.

Table 11 - Analyses window definition for participants assigned to PK - Schedule B

Scheduled visit post baseline	Targeted study day	Analysis window in study days
Week 2 (Visit 3B)	15	2 to 50
Week 12 (Visit 4)	85	51 to 127
Week 24 (Visit 5 – EOT)	169	128 to 211
Week 36 (Visit 6 – EOS)	253	≥212

Study days are calculated considering Day 1 as the day of first administration of intervention.

Table 12 - Analyses window definition for participants following the Schedule of Activities from initial version of the protocol dated of 30-Mar-2022

Scheduled visit post baseline	Targeted study day	Analysis window in study days
Week 1 (Visit 3)	8	2 to 11
Week 2 (Visit 4)	15	12 to 22
Week 4 (Visit 5)	29	23 to day 57
Week 12 (Visit 6)	85	58 to day 127
Week 24 (Visit 7 – EOT)	169	128 to 211
Week 36 (Visit 8 – EOS)	253	≥212

Study days are calculated considering Day 1 as the day of first administration of intervention.

Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, biomarker and ADA will be used for computation of baseline, the last on-treatment value and analysis according to PCSAs. They will also be included in the by-visit summaries if they are re-allocated to scheduled visits.

5.5 APPENDIX 5 PCSA

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
Vital Signs			Ref.: Kidney Disease Outcomes Quality Initiatives (KDOQI) Guideline 13; 1996; The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents, Pediatrics 2004; Bowman E & Fraser S Neonatal Handbook 2012; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009; Pediatric respiratory rates http://www.health.ny.gov/
SBP	Birth/0 to 27 days old (Neonates)	≤60 mmHg and decrease from baseline ≥20 mmHg ≥85 mmHg and increase from baseline ≥20 mmHg	Based on definition of Hypertension as average SBP or DBP ≥95th percentile for gender, age, and height on ≥3 occasions
	28 days/1 month to 23 months old (Infants)	≤70 mmHg and decrease from baseline ≥20 mmHg ≥98 mmHg and increase from baseline ≥20 mmHg	
	24 months/2 years to <6 years old (Children)	≤70 mmHg and decrease from baseline ≥20 mmHg ≥101 mmHg and increase from baseline ≥20 mmHg	
	6 to <12 years old (Children)	≤80 mmHg and decrease from baseline ≥20 mmHg ≥108 mmHg and increase from baseline ≥20 mmHg	
	12 to 16/18 years old (Adolescents)	≤90 mmHg and decrease from baseline ≥20 mmHg ≥119 mmHg and increase from baseline ≥20 mmHg	
DBP	Birth/0 to 27 days old (Neonates)	≤34 mmHg and decrease from baseline ≥10 mmHg ≥50 mmHg and increase from baseline ≥10 mmHg	
	28 days/1 month to 23 months old (Infants)	≤34 mmHg and decrease from baseline ≥10 mmHg ≥54 mmHg and increase from baseline ≥10 mmHg	
	24 months/2 years to <6 years old (Children)	≤34 mmHg and decrease from baseline ≥10 mmHg ≥59 mmHg and increase from baseline ≥10 mmHg	
	6 to <12 years old (Children)	≤48 mmHg and decrease from baseline ≥10 mmHg ≥72 mmHg and increase from baseline ≥10 mmHg	
	12 to 16/18 years old (Adolescents)	≤54 mmHg and decrease from baseline ≥10 mmHg ≥78 mmHg and increase from baseline ≥10 mmHg	
Orthostatic hypotension	All age ranges	SBP : St — Su ≤-20 mmHg DBP : St — Su ≤-10 mmHg	
Temperature	All age ranges	Rectal, ear or temporal artery: ≥100.4°F/38.0°C Oral or pacifier: ≥9.5°F/37.5°C Axillary or skin infrared: ≥99°F/37.2°C	Ear temperature not accurate below 6 months of age

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
Respiratory rate	Birth/0 to 27 days old (Neonates)	<30 per minutes >60 per minutes	Based on normal range
	28 days/1 month to 23 months old (Infants)	<24 per minutes >40 per minutes	
	24 months/2 years to <6 years old (Children)	<22 per minutes >34 per minutes	
	6 to <12 years old (Children)	<18 per minutes >30 per minutes	
	12 to 16/18 years old (Adolescents)	<12 per minutes >20 per minutes	
Sa02	All age ranges	≤95%	
Weight	All ranges	≥% weight loss from baseline	Based on identification of trends in the child's growth with a series of visits WHO Multicentre Reference Study Group, 2006; Center for Disease Control. Growth chart 2007
Clinical Chemistry			Ref Molleston JP et al. JPGN 2011; Moritz et al., Pediatrics 1999; Moritz et al., Pediatr Nephrol 2005 ; Sedlacek et al., Seminars in Dialysis 2006) Gong G et al. Clinical Biochemistry 2009; Masilamani et al. Arch Dis Children 2012; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009
ALT/SGPT	All age ranges	≥3 ULN By distribution analysis: ≥3 ULN ≥5 ULN ≥10 ULN ≥20 ULN	Based on normal ranges: 6 to 50 U/L (0-5 days), 5 to 45 U/L (1-19 years)
AST/SGOT	All age ranges	>3 ULN By distribution analysis: >3 ULN >5 ULN >10 ULN >20 ULN	Based on normal ranges: 35 to 140 U/L (0-5 days), 15 to 55 U/L (1-9 years), 5 to 45 U/L (10-19 years)
Alkaline Phosphatase	All age ranges	≥1.5 ULN	Based on normal ranges: 145 to 420 U/L (1-9 years), 130 to 560 U/L (10-11 years), 200 to 495 U/L (Boys 12-13 years), 105 to 420 U/L (Girls 12-13 years), 130 to 525 U/L (Boys 14-15 years), 70 to 130 U/L (Girls 14-15 years), 65 to 260 U/L (Boys 16-19 years), 50 to 130 U/L (Girls 16-19 years)

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
Total Bilirubin	All age ranges	≥1.3 ULN	CF = mg x 1.7 = µmol Based on normal ranges: <6 mg/dL (Term 0-1 day), <8 mg/dL (Term 1-2 days), <12 mg/dL (Term 3-5 days), <1 mg/dL (Term >5 days)
Conjugated Bilirubin	All age ranges	>35% total bilirubin and TBILI ≥1.3 ULN	CF = mg x 1.7 = µmol Based on normal range: 0 to 0.4 mg/dL
ALT and Total Bilirubin	All age ranges	ALT ≥3 ULN and Total Bilirubin ≥2 ULN	
CPK	All age ranges	≥3 ULN	
Creatinine	Birth/0 to <6 years old (Neonates, Infants, Children)	>53 µmol/L or 0.6 mg/dL	CF = mg x 8.8 = µmol Based on normal ranges: ≤0.6 mg/dL (0-1 year), 0.5 to 1.5 mg/dL (1 to 16/18 years)
	6 years to <12 years old (Children)	>90 µmol/L or 1.1mg/dL	
	12 years to 16/18 years old (Adolsecents)	>132 µmol/L or 1.5mg/dL	
Creatinine Clearance	All age ranges	50% of normal <60 mL/min/1.73m2 (After 1 year old)	Based on GFR Bedside Schwartz Formula Based on normal ranges: 20 to 50 (<8 days), 25 to 80 (8 days to 1 month), 30 to 90 (1-6 months), 40 to 115 (6-12 months), 60 to 190 (12-23 months), 90 to 165 (2-12 years), 80-120 (After 12 years)
Uric Acid	All age ranges	≤2.0 mg/dL or 119 µmol/L ≥8.0 mg/dL or 476 µmol/L	CF = mg x 5.95 = µmol Based on normal ranges: 2.4 to 6.4 mg/dL
Blood Urea Nitrogen (BUN)	Birth/0 to 27 days old (Neonates)	≥4.3 mmol/L or 12 mg/dL	CF = g x 16.66 = mmol Based on normal ranges: 3 to 12 mg/dL (NN; 5 to 18 mg/dL (other classes of age)
	28 days/1 month to 16/18 years old (Infants, Children, Adolescents)	≥6.4 mmol/L or 18 mg/dL	
Chloride	All age ranges	≤80 mmol/L or 80 mEq/L ≥115 mmol/L or 115 mEq/L	CF = 1 Based on normal range: 98 to 106
Sodium	All age ranges	≤129 mmol/L or 129 mEq/L ≥150 mmol/L or 150 mEq/L	CF = 1 Based on normal range : 134 to 146
Potassium	Birth/0 to 27 days old (Neonates)	≤3.0 mmol/L or 3.0 mEq/L ≥7.0 mmol/L or 7.0 mEq/L	CF = 1 Based on normal ranges: 3.0 to 7.0 (NN); 3.5 to 6.0 (Infants); 3.5 to 5.0 (>Infants)
	28 days/1 month to 23 months old (Infants)	≤3.5 mmol/L or 3.5 mEq/L ≥6.0 mmol/L or 6.0 mEq/L	
	24 months/2 years to 16/18 years old (Children, Adolescents)	≤3.5 mmol/L or 3.5 mEq/L ≥5.5 mmol/L or 5.5 mEq/L	
Bicarbonate	All age ranges	≤16 mmol/L or 16 mEq/L ≥30 mmol/L or 30 mEq/L	CF = 1 Based on normal range: 18 to 26

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
Calcium total	All age ranges	≤2.0 mmol/L or 8.0 mg/dL ≥2.9 mmol/L or 11.6 mg/dL	CF = mg x 0.025 = mmol Based on normal range: 8.4 to 10.9 mg/dL
Calcium ionized	All age ranges	≤1.0 mmol/L or 4.0 mg/dL ≥1.4 mmol/L or 5.6 mg/dL	CF = mg x 0.025 = mmol Based on normal range: 4.0 to 5.1 mg/dL
Total Cholesterol	All age ranges	≥6.20 mmol/L or 240 mg/dL	CF = g x 2.58 = mmol Based on normal ranges: 45 to 182 mg/dL (1-3 years), 109 to 189 mg/dL (4-6 years), 126 to 191 mg/dL (Boys 6-9 years), 122 to 209 mg/dL (Girls 6-9 years), 130 to 204 mg/dL (Boys 10-14 years), 124-217 mg/dL (Girls 10-14 years), 114 to 198 mg/dL (Boys 15-19 years), 125 to 212 mg/dL (Girls 14-19 years)
Triglycerides	All age ranges	≥4.0 mmol/L or 350 mg/dL	After >12 hours of fast) CF = g x 1.14 = mmol Based on normal ranges: 30 to 86 mg/dL (Boys 0-5 years), 32 to 99 mg/dL (Girls 0-5 years), 31-108 mg/dL (Boys 6-11 years), 35 to 114 mg/dL (Girls 6-11 years), 36 to 138 mg/dL (Boys 12-15 years), 43 to 138 mg/dL (Girls 12-15 years), 40 to 163 mg/dL (Boys 16-19 years), 40-128 mg/dL (Girls 16-19 years)
Lipasemia	All age ranges	≥2 ULN	Based on normal ranges: 3 to32 U/L (1-18 years)
Amylasemia	All age ranges	≥2 ULN	Based on normal ranges: 10 to 30 U/L (NN), 10 to 45 U/L (1-18 years)
Glucose	All age ranges	Hypoglycaemia <2.7 mmol/L or 50 mg/dL Hyperglycaemia ≥7 mmol/L or 120 mg/dL (fasted after >12 hours of fast); ≥10.0 mmol/L or 180 mg/dL (unfasted)	CF = g x 5.55 = mmol Based on normal ranges: 50 to 90 mg/dL (NN), 60 to 100 mg/dL (Child)
CRP	All age ranges	>2 ULN or >10 mg/L (if ULN not provided)	Based on normal ranges: <6 mg/L
Hematology			Common Terminology Criteria for Adverse Events v3.0 (CTCAE), 2006; Division of Microbiology and Infections Diseases Pediatric Toxicity Tables, 2007 ; Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, 2004; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009; Family Practice Notebook, LLC, 2012; Tietz NW et al. Clinical Guide to Laboratory Testing, 3rd edition 1995

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
WBC	Birth/0 to 27 days old (Neonates)	<4.0 GIGA/L or 4,000 /mm3 >25.0 GIGA/L or 25,000 /mm3	To be used if no differential count available Based on normal ranges: 9,000 to 30,000 /mm3 (birth), 9,400 to 38,000 /mm3 (0-1 day), 5,000 to 21,000 /mm3 (1 day-1 month), 6,000 to 17,500 /mm3 (1 month-2 years), 5,000 to 17,000 /mm3 (2-6 years), 4,500 to 15,500 /mm3 (6-11 years), 4,500 to 13,500 /mm3 (11-18 years)
	28 days/1 month to 23 months old (Infants)	<4.0 GIGA/L or 4,000 /mm3 >20.0 GIGA/L or 20,000 /mm3	
	24 months/2 years to <6 years old (Children)	<3.0 GIGA/L or 3,000 /mm3 >16.0 GIGA/L or 16,000 /mm3	
	6 to <12 years old (Children)	<5.0 GIGA/L or 5,000 /mm3 >17.0 GIGA/L or 17,000 /mm3	
	12 to 16/18 years old (Adolescents)	<4,5 GIGA/L or 5,000 /mm3 >13.5 GIGA/L or 17,000 /mm3	
Lymphocytes (ALC)	Birth/0 to 27 days old (Neonates)	<1.2 GIGA/L or 1,200 /mm3 >17.0 GIGA/L or 17,000 /mm3	Based on normal ranges: 2,000 to 11,500 /mm3 (0-1 days), 2,000 to 17,000 /mm3 (2 days-1 month), 3,000 to 13,500 /mm3 (1 month-2 years), 1,500 to 9,500 /mm3 (2-6 years), 1,500 to 8,000 /mm3 (6-10 years), 1,200 to 5,200 /mm3 (10-18 years)
	28 days/1 month to 23 months old (Infants)	<2.0 GIGA/L or 2,000 /mm3 >13.5 GIGA/L or 13,500 /mm3	
	24 months/2 years to <6 years old (Children)	<1.0 GIGA/L or 1,000 /mm3 >9.5 GIGA/L or 9,500 /mm3	
	6 to <12 years old (Children)	<1.0 GIGA/L or 1,000 /mm3 >8.0 GIGA/L or 8,000 /mm3	
	12 to 16/18 years old (Adolescents)	<0.6 GIGA/L or 600 /mm3 >6.0 GIGA/L or 6,000 /mm3	
Absolute Neutrophil Count (ANC)	Birth/0 to 27 days old (Neonates)	<4.0 GIGA/L or 4,000 /mm3 (1 day old) <1.5 GIGA/L or 1,500 /mm3 (2-7 days old) <1.25 GIGA/L or 1,250 /mm3 (>7 day-1 month old) >1 ULN	Based on normal ranges: 5,000 to 28,000 /mm3 (0-1 day), 1,000 to 10,000 (1 day-1 month), 1,000 to 8,500 (1-12 months), 1,500 to 8,500 (1 to 6 years), 1,500 to 8,000 (6 to 10 years), 1,800 to 8,000 (10 to 18 years)
	28 days/1 month to 23 months old (Infants)	<1.0 GIGA/L or 1,000/mm3 (1-3 months) <1.2 GIGA/L or 1,200 /mm3 (3-24 months) >1 ULN	
	24 months/2 years to <6 years old (Children)	<1.2 GIGA/L or 1,200 /mm3 >1 ULN	
	6 to <12 years old (Children)	<1.2 GIGA/L or 1,200 /mm3 >1 ULN	
	12 to 16/18 years old (Adolescents)	<1.2 GIGA/L or 1,200 /mm3 >1 ULN	
Eosinophils	All age ranges	>0.5 GIGA/L or 500 /mm3 Or >ULN if ULN >0.5 GIGA/L or 500 /mm3	Based on normal ranges: 0 to 500 /mm3 (0-1 month), 0 to 300 /mm3 (1 month-18 years)
Hemoglobin	Birth/0 to 27 days old (Neonates)	<86 mmol/L or 12.0 g/dL or any decrease ≥0.31 mmol/L or 2 g/dL	CF = g × 1.55 = mmol Based on normal ranges: 15 to 20 g/dL (0-3 days), 12.5 to 18.5 g/dL (1-2 weeks), 10.0 to 13.0 g/dL (1-6 months), 10.5 to 13.0 g/dL (7 months-2 years), 11.5 to 13.0 g/dL (2-5 years), 11.5 to 14.5 (5-8 years), 12.0 to 15.2 g/dL (13-18 years)
	28 days/1 month to 23 months old (Infants)	<1.40 mmol/L or 9.0 g/dL or any decrease ≥0.31 mmol/L or 2 g/dL	
	24 months/2 years to <16/18 years old (Children, Adolescents)	<1.55 mmol/L or 10.0 g/dL or any decrease ≥0.31 mmol/L or 2 g/dL	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
Hematocrit	Birth/0 to 27 days old (Neonates)	<0.39 l/l or 40% >0.61 l/l or 47%	CF = % × 0.01 = l/l Based on normal ranges: 45 to 61% (0-3 days), 39 to 57% (1-2 weeks), 29 to 42% (1-6 months), 33 to 38% (7 months-2 years), 34 to 39% (2-5 years), 35 to 42% (5-8 years); 36 to 47% (13-18 years)
	28 days/1 month to 23 months old (Infants)	<0.29 l/l or 29% >0.42 l/l or 42%	
	24 months/2 years to <16/18 years old (Adolescents)	<0.32 l/l or 32% >0.47 l/l or 47%	
Platelets	All age ranges	<100 GIGA/L or 100,000 /mm3 >700 GIGA/L or 700,000 /mm3	Based on normal ranges: 250,000 to 450,000 /mm3 (NN); 300,000 to 700,000 /mm3 (1-6 months), 250,000 to 600,00 /mm3 (7 months-2 years), 250,000 to 550,000 /mm3 (2-12 years), 150,000 to 450,000 /mm3 ((13-18 years)
Urinalysis			Patel HP, Pediatr Clin N Am, 2006
Ketonuria	All age ranges	Presence	Semi-quantitative methods
Glycosuria	All age ranges	Presence	Semi-quantitative methods
Hematuria	All age ranges	≥1+	Semi-quantitative methods
Proteinuria	All age ranges	≥1+	Semi-quantitative methods

5.6 APPENDIX 6 Day ranges for calculating ISS7 and HSS7 weekly scores

Table 13 - Day ranges for calculating ISS7 and HSS7 weekly scores

Analysis visit	Day range for calculating weekly score	Target day
Week 1	2-8	8
Week 2	9-15	15
Week 3	16-22	22
Week 4	23-29	29
Week 5	30-36	36
Week 6	37-43	43
Week 7	44-50	50
Week 8	51-57	57
Week 9	58-64	64
Week 10	65-71	71
Week 11	72-78	78
Week 12	79-85	85
Week 13	86-92	92
Week 14	93-99	99
Week 15	100-106	106
Week 16	107-113	113
Week 17	114-120	120
Week 18	121-127	127
Week 19	128-134	134
Week 20	135-141	141
Week 21	142-148	148
Week 22	149-155	155
Week 23	156-162	162
Week 24	163-169	169
Week 25	170-176	176
Week 26	177-183	183
Week 27	184-190	190
Week 28	191-197	197
Week 29	198-204	204
Week 30	205-211	211
Week 31	212-218	218
Week 32	219-225	225
Week 33	226-232	232
Week 34	233-239	239
Week 35	240-246	246
Week 36	247-253	253

5.7 APPENDIX 7 SELECTION CRITERIA FOR AE GROUPINGS

Table 14 - List of PTs for CMQs

Grouping	Preferred Term/ Medication Code	Preferred Term/ Medication
Conjunctivitis	10001257	Adenoviral conjunctivitis
Conjunctivitis	10010725	Conjunctival irritation
Conjunctivitis	10010726	Conjunctival oedema
Conjunctivitis	10010736	Conjunctival ulcer
Conjunctivitis	10010741	Conjunctivitis
Conjunctivitis	10010744	Conjunctivitis allergic
Conjunctivitis	10010745	Conjunctivitis chlamydial
Conjunctivitis	10010749	Conjunctivitis gonococcal neonatal
Conjunctivitis	10010754	Conjunctivitis tuberculous
Conjunctivitis	10010755	Conjunctivitis viral
Conjunctivitis	10018258	Giant papillary conjunctivitis
Conjunctivitis	10021629	Inclusion conjunctivitis
Conjunctivitis	10030861	Ophthalmia neonatorum
Conjunctivitis	10048908	Seasonal allergy
Conjunctivitis	10049458	Herpes simplex virus conjunctivitis neonatal

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