Statistical Analysis Plan for Study M22-000

A Phase 3b/4 Randomized, Blinded, Treat-to-Target and Dose-Flexibility Study of Upadacitinib in Adult Subjects with Moderate to Severe Atopic Dermatitis (Flex-Up)

Version 2.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for ABT-494 Study M22-000 (Flex-Up) "A Phase 3b/4 Randomized, Blinded, Treat-to-Target and Dose-Flexibility Study of Upadacitinib in Adult Subjects with Moderate to Severe Atopic Dermatitis (Flex-Up)."

This study aims to provide descriptive data on the efficacy and safety of dose escalation to upadacitinib 30 mg once daily (QD) and dose reduction to upadacitinib 15 mg QD based on a clinical response after 12 weeks of treatment. This data will inform the clinical management for subjects with moderate to severe AD treated with both approved doses of upadacitinib.

The analyses of pharmacodynamic biomarker endpoints will not be covered in this SAP.

The SAP will not be updated in case of administrative changes or amendments to the protocol unless the changes impact the analysis.

Unless noted otherwise, all analyses will be performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC 27513) or later under the UNIX operating system.

2.0 Study Objectives and Design

2.1 Study Objectives, Hypotheses and Estimands

The primary study objectives are:

1. Sub-Study 1 (SS1): The primary study objective for SS1 is to evaluate the efficacy and safety of dose escalation to upadacitinib 30 mg QD in subjects who do not achieve Eczema Area and Severity Index (EASI) 90 on upadacitinib 15 mg QD after 12 weeks.
2. Sub-Study 2 (SS2): The primary study objective for SS2 is to evaluate the efficacy and safety of dose reduction to upadacitinib 15 mg QD in subjects who achieve EASI 90 on upadacitinib 30 mg QD after 12 weeks.

The additional objective is to generate evidence on patient impact (patient reported outcomes [PROs]) with upadacitinib treatment based on a clinical response target (EASI 90) (Treat-to-Target).

No hypothesis testing will be performed in this study.

The estimand corresponding to the primary endpoint is defined as:

- The proportion of subjects who achieve EASI 90 at Week 24, regardless of treatment discontinuation, with upadacitinib treatments (upadacitinib 15 mg or 30 mg QD) in adult subjects with moderate to severe AD.

2.2 Study Design Overview

This is a Phase 3b/4, randomized, blinded, treat-to-target, dose-flexibility, multi-center study that will evaluate upadacitinib, as monotherapy, in approximately 454 adult subjects (≥ 18 and < 65 years of age) with moderate to severe AD who are candidates for systemic therapy.

The study is comprised of a 35-day Screening Period, a 12-week double-blind period and a 12-week single-blind period. During the single-blind period, subjects will be blinded to the upadacitinib dose and EASI score evaluations.

The study treatment duration will be 24 weeks.

After the last study visit, a 30-day follow-up visit (or phone call if a visit is not possible) will be completed to determine the status of any new or ongoing AEs/SAEs and concomitant medications.

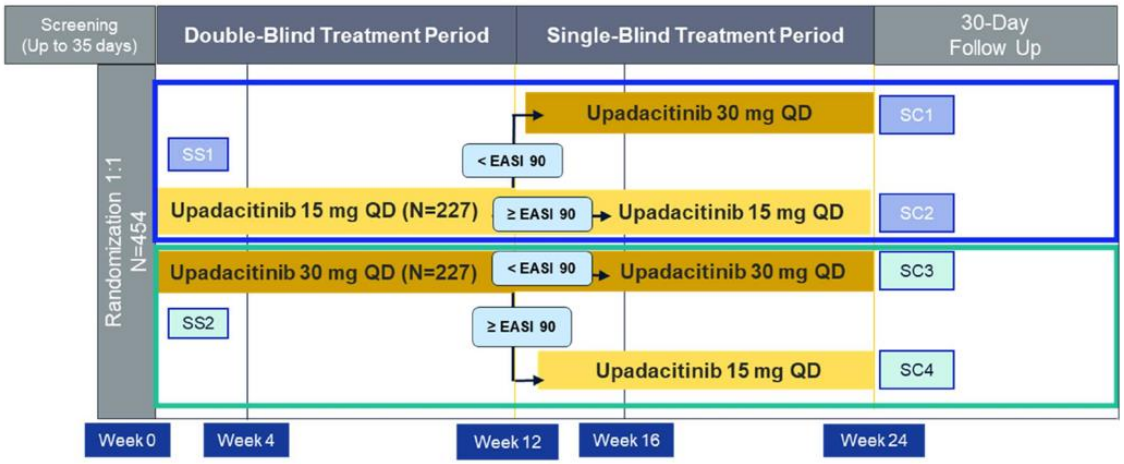
Subjects who meet the eligibility criteria will be randomized in a 1:1 ratio to enter SS1 to receive oral doses of upadacitinib 15 mg QD at Baseline or SS2 to receive oral doses of upadacitinib 30 mg QD at Baseline.

- SS1:
  - Subjects randomized to enter the SS1 at Baseline will receive oral doses of upadacitinib 15 mg QD during the 12-week double-blind period.
  - At Week 12, subjects from SS1 receiving upadacitinib 15 mg QD will be reassigned based on their EASI response, which is calculated based on the observed EASI value regardless of use of rescue medications:
    - Subjects achieving a < 90% reduction in EASI (< EASI 90) will be allocated to receive oral doses of upadacitinib 30 mg QD. This constitutes the Study Cohort 1 (SC1).
    - Subjects achieving a ≥ 90% reduction in EASI (≥ EASI 90) will continue to receive oral doses of upadacitinib 15 mg QD. This constitutes the Study Cohort 2 (SC2).
- SS2:
  - Subjects randomized to enter SS2 at Baseline will receive oral doses of upadacitinib 30 mg QD during the 12-week double-blind period.
  - At Week 12, subjects from SS2 receiving upadacitinib 30 mg QD will be reassigned based on their EASI response, which is calculated based on the observed EASI value regardless of use of rescue medications:
    - Subjects achieving < EASI 90 will continue to receive oral doses of upadacitinib 30 mg QD. This constitutes the Study Cohort 3 (SC3).
    - Subjects achieving ≥ EASI 90 will be allocated to receive oral doses of upadacitinib 15 mg QD. This constitutes the Study Cohort 4 (SC4).

The final and only database lock will occur at the end of the study.

The schematic of the study is shown in Figure 1.

Figure 1. Study Schematic



EASI = Eczema Area and Severity Index; QD = once daily; SS1 = Sub-Study 1; SS2 = Sub-Study 2; SC1 = Study Cohort 1; SC2 = Study Cohort 2; SC3 = Study Cohort 3; SC4 = Study Cohort 4

Note: The study will be stratified by Baseline vIGA-AD categories (3; 4) and prior use of dupilumab (yes; no).

2.3 Treatment Assignment and Blinding

All subjects will be assigned a unique identification number by the IRT at the screening visit. For subjects who rescreen, the screening number assigned by the IRT at the initial screening visit should be used. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule generated by the statistics department at AbbVie. Subjects in the study will be randomized in a 1:1 ratio to one of the 2 treatment groups:

- Upadacitinib 15 mg QD
- Upadacitinib 30 mg QD

The study will be stratified by Baseline vIGA-AD categories (3; 4) and prior use of dupilumab (yes; no).

During the 12-week double-blind period, study sites and subjects will remain blinded. During the single blind period, only the subjects will be blinded to the upadacitinib dose and the EASI score evaluations.

2.4 Sample Size Determination

By Assuming:

- In SS1, 54% of subjects would be EASI 90 non-responder at Week 12.
- In SS2, 65% of the subjects would be EASI 90 responder at Week 12.
- There would be no more than 8% dropouts every 12 weeks.

A total sample size of 454 subjects will result in at least 96 subjects in SC1 and SC4, to ensure the half width of 95% CI will be within 10% for EASI 90 response estimation at Week 24.

3.0 Endpoints

3.1 Primary Endpoint

The primary endpoint is:

- Achievement of EASI 90 at Week 24.

3.2 Secondary Endpoints

The secondary endpoints are:

- Achievement of EASI 75/100 at Week 24.
- Achievement of EASI 75/90/100 at Week 12.
- Achievement of EASI 90 and a Worst Pruritus NRS of 0 or 1 for subjects with Worst Pruritus NRS > 1 at Baseline at Week 12 and Week 24.
- Achievement of vIGA-AD of 0 or 1 at Week 12.
- Achievement of vIGA-AD of 0 or 1 at Week 24

- Achievement of an improvement (reduction) in Worst Pruritus NRS ≥ 4 for subjects with Worst Pruritus NRS ≥ 4 at Baseline at Week 12.
- Achievement of an improvement (reduction) in Worst Pruritus NRS ≥ 4 for subjects with Worst Pruritus NRS ≥ 4 at Baseline at Week 24.
- Achievement of Worst Pruritus NRS of 0 or 1 for subjects with Worst Pruritus NRS > 1 at Baseline at Week 12.
- Achievement of Worst Pruritus NRS of 0 or 1 for subjects with Worst Pruritus NRS > 1 at Baseline at Week 24.
- Achievement of an improvement (reduction) from Baseline in DLQI ≥ 4 for subjects with DLQI ≥ 4 at Baseline at Week 12.
- Achievement of an improvement (reduction) from Baseline in DLQI ≥ 4 for subjects with DLQI ≥ 4 at Baseline at Week 24.
- Achievement of DLQI 0/1 for subjects with DLQI > 1 at Baseline at Week 12.
- Achievement of DLQI 0/1 for subjects with DLQI > 1 at Baseline at Week 24.

3.3 Additional Efficacy Endpoints

All variables listed as primary or secondary endpoints will be analyzed at all applicable visits other than those listed above. In addition, the following endpoints will be evaluated at all applicable visits unless otherwise specified. Additional Efficacy Endpoints are:

- Experience of a loss of response after Week 12 until Week 24 (defined as a loss of at least 50% of the EASI improvement gained from Baseline to Week 12) among subjects who had an EASI 90 response at Week 12.
- Achievement of EASI score < 7 / < 3 / < 1.
- Achievement of Worst Pruritus NRS of 0 for subjects with Worst Pruritus NRS >0 at Baseline.
- Achievement of an improvement (reduction) in Patient Oriented Eczema Measure (POEM) ≥ 4 from Baseline for subjects with POEM ≥ 4 at Baseline.
- Achievement of POEM ≤ 2 / 0 for subjects with POEM > 2 / > 0 at Baseline, respectively.

- Achievement of POEM Itch item score of 0 for subjects with POEM Itch item score >0 at Baseline.
- Achievement of POEM Sleep item score of 0 for subjects with POEM Sleep item score > 0 at Baseline.
- Change and percent change from Baseline in Patient Global Impression of Severity (PGIS).
- Achievement of "Minimal" or "Absent" on the PGIS for subjects who are "Mild" or worse on the PGIS at Baseline.
- Achievement of "Absent" on the PGIS for subjects who are "Minimal" or worse on the PGIS at Baseline.
- Change and percent change from Baseline in Patient Global Impression of Treatment (PGIT).
- Achievement of "Extremely satisfied" or "Very satisfied" on the PGIT for subjects who are "Somewhat satisfied" or worse on the PGIT at Baseline.
- Achievement of "Extremely Satisfied" on the PGIT for subjects who are "Very satisfied" or worse on the PGIT at Baseline.
- Achievement of an improvement (reduction) in Atopic Dermatitis Impact Scale (ADerm-IS) Sleep ≥ 12 from Baseline for subjects with ADerm-IS Sleep ≥ 12 at Baseline.
- Achievement of an improvement (reduction) in ADerm-IS Emotional State ≥ 11 from Baseline for subjects with ADerm-IS Emotional State ≥ 11 at Baseline.
- Achievement of an improvement (reduction) in ADerm-IS Daily Activities ≥ 14 from Baseline for subjects with ADerm-IS Daily Activities ≥ 14 at Baseline.
- Achievement of ADerm-IS Sleep ≤ 3 / 0 for subjects with ADerm-IS Sleep > 3/> 0 at Baseline, respectively.
- Achievement of ADerm-IS Daily Activities ≤ 2 / 0 for subjects with ADerm-IS Daily Activities > 2/> 0 at Baseline, respectively.
- Achievement of ADerm-IS Emotional State ≤ 2 / 0 for subjects with ADerm-IS Emotional State > 2/> 0 at Baseline, respectively.

- Achievement of an improvement (reduction) in Atopic Dermatitis Symptom Scale (ADerm-SS) Skin Pain ≥ 4 from Baseline for subjects with ADerm-SS Skin Pain ≥ 4 at Baseline.
- Achievement of ADerm-SS Skin Pain ≤ 1 / 0 for subjects with ADerm-SS Skin Pain > 1/> 0 at Baseline, respectively.
- Achievement of an improvement (reduction) in ADerm-SS 7-item total symptom score (TSS-7) ≥ 28 from Baseline for subjects with ADerm-SS TSS-7 ≥ 28 at Baseline.
- Achievement of ADerm-SS TSS-7 ≤ 11 / ≤ 1 for subjects with ADerm-SS TSS-7 > 11 / > 1 at Baseline, respectively.
- Achievement of EASI 75 / 90, for subjects who experienced an inadequate response to previous treatment with dupilumab for AD as reported by the investigator
- Achievement of EASI 90 and a Worst Pruritus NRS of 0 or 1, for subjects with Worst Pruritus NRS > 1 at Baseline and experienced an inadequate response to previous treatment with dupilumab for AD as reported by the investigator.
- Achievement of EASI 75 / 90, for subjects who were previously treated with dupilumab for AD.
- Achievement of EASI 90 and a Worst Pruritus NRS of 0 or 1, for subjects with Worst Pruritus NRS > 1 at Baseline and were previously treated with dupilumab for AD.
- For subjects participating in the Wearable Tool Substudy:
  - Change from Baseline in average nightly nocturnal scratch: total scratch time and number of scratch events.
  - Change from Baseline in the following sleep parameters: total sleep time, wake after sleep onset, sleep efficiency, and sleep onset latency.

3.4 Safety Endpoint(s)

The following endpoints will be included in the safety analyses:

- Treatment emergent adverse events (TEAEs);

- Serious adverse events (SAEs);
- Adverse events of special interest (AESIs);
- Adverse events (AEs) leading to discontinuation;
- Vital signs and laboratory tests.

Laboratory assessments will include hematologic parameters, chemistry, liver function tests, and lipid parameters.

4.0 Analysis Populations

For simplicity, the double-blind period and the single-blind period are denoted by DB period and SB period respectively. The following population sets will be used for the analyses.

The Intent-to-Treat (ITT) Populations for the efficacy analyses are defined as:

- ITT Population of SS1 in DB Period (ITT 1 SS1 Population) includes all subjects who are randomized into SS1.
- ITT Population of SS1 in SB Period (ITT 2 SS1 Population) includes all subjects who are randomized into SS1 at Baseline and continued into SB Period.
- ITT Population of SS2 in DB Period (ITT 1 SS2 Population) includes all subjects who are randomized into SS2.
- ITT Population of SS2 in SB Period (ITT 2 SS2 Population) includes all subjects who are randomized into SS2 at Baseline and continued into SB Period.

The Safety Populations for the safety analyses are defined as:

- Safety Population of SS1 in DB Period (Safety 1 SS1 Population) consists of all subjects who are randomized into SS1 and received at least 1 dose of study drug in DB Period.

- Safety Population of SS1 in SB Period (Safety 2 SS1 Population) consists of all subjects who received at least 1 dose of study drug in SB Period of SS1.
- Safety Population of SS2 in DB Period (Safety 1 SS2 Population) consists of all subjects who are randomized into SS2 and received at least 1 dose of study drug in DB Period.
- Safety Population of SS2 in SB Period (Safety 2 SS2 Population) consists of all subjects who received at least 1 dose of study drug in SB Period of SS2.
- Safety Population for all upadacitinib treatment (ALL UPA Population) consists of all subjects who received at least 1 dose of upadacitinib in the study. This population includes two cohorts: All UPA 15 mg and All UPA 30 mg. All UPA 15 mg cohort consists of all subjects who received at least 1 dose of upadacitinib 15 mg in SS1 and SS2 (only count exposure to 15 mg). All UPA 30 mg consists of all subjects who received at least 1 dose of upadacitinib 30 mg in SS1 and SS2 (only count exposure to 30 mg). All safety analysis based on ALL UPA Population will be summarized by the above two cohorts.

These populations will be used to provide a comprehensive summary of safety based on treatment received regardless of randomization.

Table 1. Analyses Populations: ITT Populations and Safety Populations

Analyses Populations	Study Period	Analyses Groups
ITT 1 SS1	DB Period	UPA 15 mg QD
ITT 1 SS2		UPA 30 mg QD
ITT 2 SS1	SB Period	UPA 15/15 mg QD
		UPA 15/30 mg QD
ITT 2 SS2		UPA 30/15 mg QD
		UPA 30/30 mg QD
Safety 1 SS1	DB Period	UPA 15 mg QD
Safety 1 SS2		UPA 30 mg QD
Safety 2 SS1	SB Period	UPA 15/15 mg QD
		UPA 15/30 mg QD
Safety 2 SS2		UPA 30/15 mg QD
		UPA 30/30 mg QD
ALL UPA	During the upadacitinib administration	All UPA 15 mg QD
		All UPA 30 mg QD

5.0 Subject Disposition

In the DB Period, the number of subjects for each of the following categories will be summarized overall and by the two sub-studies in the ITT 1 Populations:

- Subjects randomized
- Subjects randomized and dosed in DB Period
- Subjects who completed DB Period
- Subjects who completed study drug in DB Period
- Subjects who prematurely discontinued study in DB Period
- Subjects who prematurely discontinued study drug in DB Period
- Subjects who initiated rescue medications in DB Period

The summary will be provided for SB Period for each of the following categories by the four study cohorts in the ITT 2 Populations:

- Subjects who entered SB Period
- Subjects dosed in SB Period
- Subjects who completed SB Period
- Subjects who completed study drug in SB Period
- Subjects who prematurely discontinued study in SB Period
- Subjects who prematurely discontinued study drug in SB Period
- Subjects who initiated the rescue medications in SB Period

6.0 Study Treatment Duration and Compliance

For the DB Period and the SB Period, the duration of treatment will be summarized by sub-studies and treatment groups using Safety 1 and Safety 2 Populations, respectively.

DB Period:

- For subjects who did not continue into SB Period:
  - Date of last dose of study drug in DB Period Date of first dose of study drug in DB Period + 1.
- For subjects who continued into SB Period:
  - Minimum of (Date of first dose of study drug in SB Period Date of first dose of study drug in DB Period, Date of last dose of study drug in DB Period Date of first dose of study drug in DB Period + 1.)

SB Period:

For subjects who continued into SB Period:

- Date of last dose of study drug in SB Period Date of first dose of study drug in SB Period + 1.

ALL UPA:

Study drug duration during the administration of study drug in ALL UPA Population is defined as follows.

For All UPA 15mg cohort:

- Date of last dose of upadacitinib 15mg Date of first dose of upadacitinib 15 mg + 1.

For All UPA 30mg cohort:

- Date of last dose of upadacitinib 30mg Date of first dose of upadacitinib 30 mg + 1.

Duration of treatment will be summarized using the number of subjects treated, mean, standard deviation, median, minimum and maximum. In addition, the number and percentage of subjects in each treatment duration intervals (≥ 4 weeks, ≥ 12 weeks, ≥ 16 weeks, and achieving 24 weeks) will be summarized for Safety 1, Safety 2, and All UPA Populations.

Treatment compliance for DB Period and SB Period will be summarized by treatment groups for Safety 1, and Safety 2 Populations. Treatment compliance is defined as the number of tablets actually taken divided by the number of tablets that should have been taken. For subjects who prematurely discontinued the study drug, the planned tablets will only be counted prior to that scheduled visit of discontinuation. Percent compliance will be summarized.

7.0 Subject Characteristics

7.1 Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be summarized for each treatment in each ITT 1 Population.

Demographics:

- Sex (female, male)
- Age (years)
- Age categories (18 to < 40; ≥ 40 to < 65 years).
- Race (White, Black or African American, Asian, American Indian/Alaska Native, Native Hawaiian or Other Pacific Islander)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Body Weight (kg)
- Tobacco/Nicotine and Alcohol Use:
  - Tobacco/Nicotine Use (unknown, never, current, former)
  - Alcohol Use (unknown, never, current, former)

Baseline Characteristics

- Baseline EASI (< median; ≥median)
- Baseline EASI (<21; ≥21)
- EASI overall score and body region scores
- Body Surface Area (BSA)
- Baseline vIGA-AD (3, 4)
- Previous systemic therapy for AD (with and without)
- Prior Atopic Dermatitis Treatment
- Worst Pruritus NRS (Weekly Average)
- DLQI, POEM, PGIS, PGIT
- ADerm-IS sleep domain, daily activity domain, and emotional state domain
- ADerm-SS Skin pain and TSS-7
- Prior use of dupilumab
- Disease duration since diagnosis (years)
- Disease duration since symptoms started (years)
- Duration between symptoms and diagnosis (years)

Clinical Test at Screening

- TB Status: Tuberculin PPD skin test result, QuantiFERON-TB Gold test result, Latent TB (Yes/No)
- Hepatitis B Virus (HBV)/Hepatitis C Virus (HCV)
- Chest x-ray
  - Normal, Abnormal
  - Calcified granulomas (Absent, Present)
  - Pleural scarring (Absent, Present)
  - Pleural thickening (Absent, Present)
  - Indicative of previous TB infection (Yes, No)

7.2 Medical History and Prior and Concomitant Medications

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report. The number and percentage of subjects in each medical history category (by MedDRA system organ class (SOC) and preferred term) will be summarized overall and by treatment group for the safety 1 Populations. The SOC will be presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each SOC. Subjects reporting more than one condition/diagnosis will be counted only once in each row (SOC or preferred term).

A prior medication is defined as any medication taken prior to the date of the first dose of study drug. Prior medications will be summarized in the ITT 1 Populations.

Concomitant medications will be summarized by periods in each Safety 1 and Safety 2 Populations.

- A concomitant medication in DB Period is defined as any medication that started prior to the date of the first dose of study drug in DB Period and continued to be taken after the first dose of study drug in DB Period; or any

medications taken after the first dose of study drug and within 1 day of the last dose of study drug in DB Period.

- A concomitant medication in SB Period is defined as any medication that started prior to the date of the first dose of study drug in SB Period and continued to be taken after the first dose of study drug in SB Period or any medications, other than study drug, taken after the first dose of study drug and within 1 day of the last dose of study drug in SB Period.

The number and percentage of subjects taking medications will be summarized by generic drug name based on the World Health Organization (WHO) Drug Dictionary for both prior and concomitant medications.

7.3 Protocol Deviations

Protocol deviations include eligibility criteria violations, receipt of wrong treatment or incorrect dose of study treatment, development of withdrawal criteria without being withdrawn, and use of prohibited concomitant medications. A listing of subjects with protocol deviations will be provided.

For each of the following protocol deviation categories and across all categories, the number and percentage of randomized subjects with at least one protocol deviation will be summarized overall and by the treatment groups in the ITT 1 Population:

- Subject entered into the studies or cohorts even though did not satisfy entry criteria;
- Subject developed withdrawal criteria during the study but was not withdrawn;
- Subject received wrong treatment or incorrect dose of study treatment;
- Subject took prohibited concomitant medication.

8.0 Handling of Potential Intercurrent Events for the Primary and Secondary Endpoints

For all the endpoints, no intercurrent event will be considered in the primary approach (treatment strategy policy), i.e., all observed data will be included in the analyses.

9.0 Efficacy Analyses

9.1 General Considerations

The efficacy analysis will be conducted in the ITT 1 and ITT 2 Populations in DB Period and SB Period descriptively and no statistical testing will be performed in this study.

Categorical endpoints will be summarized by counts and percentages, as well as 95% confidence interval (CI) of the percentage. Continuous variables will be analyzed by the number of observations, mean, standard deviation, median, minimum, maximum, as well as 95% confidence intervals (CIs) of the mean values. The primary missing data handling approach for efficacy summary is As Observed (AO).

Table 2. Analysis Models and Imputation Methods

Period	Type of Variables	Imputation Method	Intercurrent Events Handling	Analysis Model
DB	Categorical	AO (primary)	The treatment policy strategy is used in this study, i.e., the occurrence of the intercurrent events (e.g., treatment discontinuation, rescue etc.) are considered irrelevant in defining the treatment effect of interest. Under this strategy, all values for the variables of interest are used regardless of the intercurrent events.	Descriptive summary
	Continuous	AO (primary)		ANCOVA including DB treatment groups, baseline, stratification factors (vIGA-AD categories [3; 4] and prior use of dupilumab [yes; no]) in the model.
SB	Categorical	AO (primary)		Descriptive summary
	Continuous	AO (primary)		ANCOVA including SB treatment groups, baseline, stratification factors (vIGA-AD categories [3; 4] and prior use of dupilumab [yes; no]) in the model.

Note: Sensitivity analysis for the primary endpoint will use multiple imputation to handle missing data.

9.2 Handling of Missing Data

All efficacy endpoints will be analyzed using AO approach:

- The **AO analysis** will not impute values for missing evaluations, and thus a subject who does not have an evaluation at a scheduled visit will not be included in the AO analysis for that visit.

Another missing data handling method performed as a sensitivity analysis for the primary endpoint only is Multiple Imputation (MI) approach, which defined as below:

- **MI approach**: Markov Chain Monte Carlo (MCMC) will be first applied to augment data into monotonic missing pattern and PROC MI will be used to generate 30 datasets using the regression method. The imputation is done in two steps for the primary endpoint.

Step 1: Missing EASI scores will be imputed. The variables to be included in the imputation model are treatment groups, actual stratification factors (vIGA-AD categories (3; 4) and prior use of dupilumab (yes; no)), baseline, and measurements at each visit. The random seed for MCMC and the random seed for PROC MI are set as 1005 and 9015. The imputed post-baseline measurements will be rounded to the same precision as the observed data before the determination of responder status.

Step 2: After obtaining the EASI 90 at Week 24 based on MI imputed values, subjects will be characterized as responders or non-responders based on MI imputed datasets. The primary endpoint will be analyzed using each of the 30 datasets. SAS PROC MIANALYZE will be used to generate the final inferences of the EASI 90 percentages, the standard errors as well as 95% CIs.

9.3 Primary Efficacy Endpoint(s) and Analyses

9.3.1 Primary Efficacy Endpoint

The Primary endpoint is the achievement of EASI 90 at Week 24.

9.3.2 Main Analysis of Primary Efficacy Endpoint

Frequencies and percentages will be provided along with 95% CIs. The AO approach will be used as the primary approach for handling the missing data. The attributes of the estimand corresponding to the primary efficacy objective are summarized in Table 3.

Table 3. Summary of the Estimand Attributes Corresponding to the Primary Efficacy Objective

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
EASI 90 at Week 24	Upadacitinib 15 mg or 30 mg	Achievement of EASI 90 at Week 24	Subjects with moderate to severe atopic dermatitis	The treatment policy strategy is used in this study. All the values for the variable of interest will be used regardless of Intercurrent Events.	Counts and percentages will be provided along with 95% CIs.

Analysis of the primary endpoint will be conducted on the ITT 2 SS1 and ITT 2 SS2 Populations.

9.3.3 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoint

The primary endpoint will be summarized using the Multiple Imputation (MI) to handle missing data.

9.4 Secondary Efficacy Endpoints and Analyses

9.4.1 Secondary Efficacy Endpoints

The secondary endpoints are:

- Achievement of EASI 75/100 at Week 24.
- Achievement of EASI 75/90/100 at Week 12.
- Achievement of EASI 90 and a Worst Pruritus NRS of 0 or 1 for subjects with Worst Pruritus NRS > 1 at Baseline at Week 12 and Week 24.

- Achievement of vIGA-AD of 0 or 1 at Week 12.
- Achievement of vIGA-AD of 0 or 1 at Week 24.
- Achievement of an improvement (reduction) in Worst Pruritus NRS ≥ 4 for subjects with Worst Pruritus NRS ≥ 4 at Baseline at Week 12.
- Achievement of an improvement (reduction) in Worst Pruritus NRS ≥ 4 for subjects with Worst Pruritus NRS ≥ 4 at Baseline at Week 24.
- Achievement of Worst Pruritus NRS of 0 or 1 for subjects with Worst Pruritus NRS > 1 at Baseline at Week 12.
- Achievement of Worst Pruritus NRS of 0 or 1 for subjects with Worst Pruritus NRS > 1 at Baseline at Week 24.
- Achievement of an improvement (reduction) from Baseline in DLQI ≥ 4 for subjects with DLQI ≥ 4 at Baseline at Week 12.
- Achievement of an improvement (reduction) from Baseline in DLQI ≥ 4 for subjects with DLQI ≥ 4 at Baseline at Week 24.
- Achievement of DLQI 0/1 for subjects with DLQI > 1 at Baseline at Week 12.
- Achievement of DLQI 0/1 for subjects with DLQI > 1 at Baseline at Week 24.

9.4.2 Main Analyses of Secondary Efficacy Endpoints

Frequencies and percentages will be provided along with 95% CIs based on ITT 1 and ITT 2 populations using the AO approach. The attributes of the estimands corresponding to the secondary efficacy objectives are summarized in Table 4.

Table 4. Summary of the Estimand Attributes Corresponding to the Secondary Efficacy Objectives

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Categorical secondary endpoints	Upadacitinib 15 mg or 30 mg	Achievement of each respective categorical endpoint	Subjects with moderate severe atopic dermatitis	The treatment policy strategy is used in this study. All the values for the variable of interest will be used regardless of Intercurrent Events.	Counts and percentages will be provided along with 95% CIs

9.4.3 Sensitivity and Supplementary Analyses for Secondary Efficacy Endpoints

There is no sensitivity or supplementary analysis for secondary efficacy endpoints.

9.5 Additional Efficacy Endpoints and Analyses

The additional efficacy endpoints listed in Section 3.3 will be analyzed as below. The categorical endpoints will be summarized by ITT 1 and ITT 2 populations using the AO approach. For the categorical endpoints, counts and percentages will be provided along with 95% CIs, by visit and by treatment group. For the continuous endpoints, Least Square (LS) mean, 95% CI and standard error (SE) will be provided using ANCOVA including treatment, baseline, stratification factors (vIGA-AD categories [3; 4] and prior use of dupilumab [yes; no]) in the model.

9.6 Efficacy Subgroup Analyses

The primary endpoint will be also summarized by the following subgroups using the AO approach:

- Baseline vIGA-AD (3; 4),
- Baseline EASI score (<21; ≥21), and
- Baseline EASI score (<median; ≥median).

- Prior Use of Dupilumab (Yes; No)

9.7 Analysis of Daily Efficacy Measurement

For daily efficacy assessments of the Worst Pruritus NRS, ADerm-IS sleep domain, and ADerm-SS skin pain, a rolling weekly average is calculated by using handheld device only to represent the corresponding endpoints by week in DB Period and SB Period.

The weekly average of the daily values from a maximum of 7 days immediately prior to the first dose date will be used as the Baseline value. The rolling weekly average score is calculated for each Day m, starting from Day 8 through the Week 24 visit as follows. Let P_{m-6}, P_{m-5}, …, P_{m-1}, P_m be the daily score from Day m 6 to Day m, and N_m be the number of days with non-missing scores from Day m 6 to Day m, then the rolling weekly average for Day m is:

$$\frac{\sum_{i=m\ 6}^{m} P_i}{N_m}$$

If the values from four or more days of the 7-day period are missing, then the rolling weekly average of Day m will be set to missing. If more than one assessment is included on the same day, the assessment associated with the worst condition on that day will be chosen as the daily score. Analysis value for a given visit will be selected from rolling averages based on analysis window conventions.

10.0 Safety Analyses

10.1 General Considerations

Safety summaries will be provided using the safety Populations. For the safety analysis, subjects are assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized.

Safety analyses will include adverse events, laboratory, and vital sign measurements. Missing safety data will not be imputed.

10.2 Adverse Events

The summaries of adverse events will be provided by treatment groups in DB Period for Safety 1 Population, in SB Period for Safety 2 Population, and during the administration of upadacitinib for All UPA Population.

10.2.1 Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as follows:

- TEAEs in DB Period are defined as any adverse events that begin or worsen in severity after initiation of upadacitinib through the minimum (30 days following the last dose of upadacitinib in DB Period, or the start day of SB Period 1).
- TEAEs in SB Period are defined as any adverse events that begin or worsen in severity after initiation of upadacitinib in SB Period through 30 days following the last dose of upadacitinib in SB Period.
- TEAEs during the administration of upadacitinib are defined as any adverse events that begin or worsen in severity after initiation of upadacitinib through 30 days following the last dose of upadacitinib.

If a missing or an incomplete onset date is collected for an adverse event, the event will be assumed to be treatment-emergent unless there is other evidence that confirms that the event is not treatment-emergent (e.g., the event end date is prior to the study drug start date). Events where the onset date is the same as the study treatment start date are assumed to be treatment-emergent.

All TEAEs will be summarized overall, as well as by primary MedDRA SOC and Preferred Term. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

The number and percentage of subjects experiencing TEAEs and the number of events per 100 patient-years of exposure will be summarized.

TEAEs per 100 patient-years of exposure are defined as the number of TEAEs divided by the total exposure in 100 patient-years. See the calculation method below:

100 * (Number of TEAEs) / (Total Patient Years)

where total patient years is defined as the sum of the study drug duration (defined in Section 6.0) of all subjects normalized by 365.25 and rounded to 1 decimal place.

10.2.2 Adverse Event Overview

The number and percentage of subjects experiencing TEAEs will be summarized for each treatment group for the following AE categories:

- Any TEAE
- Any treatment-emergent serious adverse events (SAE)
- Any TEAE leading to discontinuation of study drug
- Any severe TEAE (Grade 3 and above according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0)
- Any TEAE with reasonable possibility of being drug related
- Any treatment-emergent SAE with reasonable possibility of being drug related
- Any TEAE leading to death
- All Deaths
    - Deaths occurring ≤ 30 days after last dose of upadacitinib
    - Deaths occurring > 30 days after last dose of upadacitinib
    - Related to COVID 19

In addition, a separate overview of AESIs and overview of AESIs per 100 patient-years of exposure will be provided for the categories in Section 10.2.6.

10.2.3 Treatment-Emergent Adverse Events by SOC and/or PT

TEAEs will be summarized and presented using primary MedDRA version 26.0 by system organ class (SOC) and preferred terms (PT); by maximum relationship to study drug as assessed by the investigator (e.g., reasonable possibility or no reasonable possibility) and SOC and PT; by maximum toxicity and SOC and PT. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC. Subjects reporting more than one adverse event for a given MedDRA preferred term will be counted only once for that term (most severe incident for the toxicity tables and most related incident for the relationship tables). A subject who reports more than 1 AE in different SOCs will be counted only once in the overall total. Subjects reporting more than one type of adverse event will be counted only once in the overall total. If the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

The following summaries of adverse events will be generated:

- All TEAEs
- Treatment-emergent serious adverse events
- Treatment-emergent severe adverse events
- TEAEs with reasonable possibility of being drug related
- TEAEs leading to discontinuation of study drug
- TEAEs by maximum toxicity
- TEAEs of Special Interest
- TEAEs leading to death

For summaries of AEs by toxicity, each subject is counted only once according to the maximum toxicity level observed. If a subject has an AE with an unknown toxicity, then the subject will be counted in the toxicity category of "unknown." The only exception is that if the subject has another occurrence of the same AE with the most extreme, non-fatal NCI CTCAE toxicity (i.e., grade 4) or is fatal (grade 5). In this case, the subject will be counted under grade 4 if non-fatal or 5 if fatal. For tables that look at severity instead of

toxicity, the subjects that have an unknown NCI CTCAE grade but another occurrence of the same AE that is considered severe (grade ≥ 3) will be counted under severe.

10.2.4 Treatment-Emergent Adverse Events per Patient-Years of Exposure

AEs occurring during the entire study will be presented by event rate per 100 patient years. These will be presented by treatment group for the following AE categories.

- Any TEAE
- Any treatment-emergent SAE
- Any TEAE leading to discontinuation of study drug
- Any severe TEAE
- Any TEAE with reasonable possibility of being drug related
- Any treatment-emergent SAE with reasonable possibility of being drug related
- TEAEs of Special Interest
- Any TEAE leading to death
- All Deaths
    - Deaths occurring ≤ 30 days after last dose of upadacitinib
    - Deaths occurring > 30 days after last dose of upadacitinib
    - Related to COVID 19

Additional AEs may be considered for tabulation/summary based on recommendations from Clinical and Safety as deemed appropriate.

10.2.5 Deaths, Serious Adverse Events, and Adverse Events Leading to Study Treatment Discontinuation

SAEs (including deaths) and AEs leading to study drug discontinuation will be presented in listing format. SAEs and AEs leading to study drug discontinuation will be summarized by SOC and PT.

In addition, for each treatment group, the event rate leading to per 100 patient-years of exposure will be calculated for each SOC and each PT for each treatment emergent SAE and TEAEs leading to discontinuation of study drug.

10.2.6 Adverse Events of Special Interest

Adverse events of special interest will be summarized by SOC and PT and listing format and will be based on standard or company MedDRA queries (SMQs or CMQs).

Adverse events of special interest are categorized as follows:

- Serious infections
- Opportunistic infection excluding tuberculosis and herpes zoster
- Herpes Zoster
- Active Tuberculosis
- Anemia
- Neutropenia
- Lymphopenia
- Renal Dysfunction
- Hepatic disorders (including DILI)
- Malignancy
- Non-melanoma skin cancer (NMSC)
- Malignancy excluding NMSC
- Lymphoma
- Adjudicated MACE
- Adjudicated VTE
- Adjudicated gastrointestinal perforations
- Bone fractures
- Retinal detachment
- Serious hypersensitivity reactions

Detailed information about the search criteria is provided in Appendix B.

Tabular listings of selected adverse events of special interest will be provided. Possible malignancy will only be listed.

Information on the extent of herpes zoster infection involvement will be summarized as collected in the respective AE form.

10.3 Analysis of Laboratory Data

Data collected from central and local laboratories, including additional laboratory testing due to an SAE, will be used in all analyses, except for Baseline where SAE-related laboratory assessments on or before the first dose of study drug will be excluded. The clinical laboratory tests defined in the protocol operations manual (e.g., hematology and clinical chemistry) will be summarized.

For the analysis of laboratory data, values observed up to 30 days after the last dose of upadacitinib will be included.

Analysis of Quantitative Laboratory Parameters (Hematology, Chemistry and Urinalysis)

Raw values and change from Baseline (percent change if applicable) to each applicable post-baseline visit will be summarized for selected laboratory variables in the Safety 1 and Safety 2 Populations. At each visit, the following descriptive statistics will be presented by treatment groups: number of observations, Baseline mean (Standard deviation, SD), visit mean (SD), medium, change from Baseline mean (SD), standard error, and the 95% confidence interval of the mean change from Baseline.

Shift Table Analyses

Selected laboratory parameters will be tabulated using shift tables from Baseline to the worst value by NCI CTCAE in DB Period for the Safety 1, in SB Period for the Safety 2 Population and during the administration of upadacitinib for the All UPA Population.

Selected lipid parameters will be summarized using National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) guidelines and details can be found in Appendix E. Similar shift tables will be provided to summarize shifts from Baseline to the final post-baseline value in DB Period for the Safety 1, in SB Period for the Safety 2 Population and during the administration of upadacitinib for the All UPA Population. Here, the Upadacitinib Baseline is defined as the last observation prior to the first dose of upadacitinib. The criteria in shift table are defined using CTCAE 4.03.

Potentially Clinically Important Laboratory Values

Laboratory abnormalities will be evaluated based on Potentially Clinically Important (PCI) criteria (NCI CTCAE V4.03 criteria of Grade 3 or above) in DB Period for the Safety 1, in SB Period for the Safety 2 Population and during the administration of upadacitinib for the All UPA Population. For each laboratory PCI criterion, the number and percentage of subjects who have a laboratory value meeting the criteria will be summarized. Listings will be provided to summarize subject-level laboratory data for subjects meeting PCI criteria. The PCI criteria are defined in Appendix D using CTCAE 4.03.

Liver Function Tests

For the purpose of assessing for potential Hy's law cases, the frequencies and percentages of subjects with post-baseline liver function test values that meet the PCI criteria (defined in Appendix D) will be presented in DB Period for the Safety 1 Population, in SB Period for the Safety 2 Population and during the administration of upadacitinib for the ALL UPA Population. A listing of possible Hy's Law cases will be provided.

10.4 Analysis of Vital Signs

Vital sign measurements of systolic and diastolic blood pressure, pulse rate, respiratory rate and body temperature will be summarized.

Each vital sign variable will be summarized for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from Baseline to each applicable post-baseline visit in both DB Period and SB Period will be summarized for each vital sign variable, with the number of observations, Baseline mean, and visit mean. The change from Baseline mean, standard error, and 95% confidence interval will be presented for the mean change from Baseline within each treatment group in Safety 1 and Safety 2 Populations.

Vital sign variables will be evaluated based on potentially clinically important (PCI) criteria (Appendix D) for the Safety 1, Safety 2 and the ALL UPA Population. For each vital signs PCI criterion, the number and percentage of subjects who have at least one vital sign value meeting the criteria will be summarized. Listings will be provided to summarize subject-level vital sign data for subjects meeting PCI criteria.

10.5 Safety Topics of Interest

Not applicable.

10.6 Other Safety Analyses

Not applicable.

10.7 Safety Subgroup Analyses

Not applicable.

11.0 Other Analyses

Not applicable.

12.0 Interim Analyses

There will be no interim analyses.

12.1 Data Monitoring Committee

Given no subjects participating in the study will receive placebo or other active comparators, the causality of any AEs reported in the participants can be adequately assessed in the context of upadacitinib treatment. The study team will monitor and evaluate any AEs to identify findings that could put the study participants at risk and then make clinical decisions regarding the study conduct, which could include modification or termination of the study. This can adequately safeguard the participants. Given the above, it is not necessary to implement an independent Data Monitoring Committee for the conduct of this study.

13.0 Overall Type-I Error Control

No hypothesis testing will be performed in this study. Overall type-1 error control is not considered.

14.0 Version History

Table 5. SAP Version History Summary

Version	Date	Summary
1.0	11 July 2023	Initial version
2.0	27 August 2024	1. The other events of interest in version 1 have been re-classified into the AESI category. These events include Bone fractures, Retinal detachment, and Serious hypersensitivity reactions (in Section 3.4, 10.2.3, 10.2.4, 10.2.6 and Appendix B). These changes are due to the release of the PSSAP version 8.0 on Aug. 20, 2024. 2. Added the Rescue Definition as Appendix C. 3. Made some minor changes, including typo corrections.

14.1 Changes to Planned Analyses in the Protocol

Not applicable

15.0 References

1. Graham JW, Olchowski AE, Gilreath TD. How many imputations are really needed? Some practical clarifications of multiple imputation theory. Prev Sci. 2007;8(3):206-13.
2. Rubin DB, Schenker N. Interval estimation from multiply-imputed data: a case study using agriculture industry codes. J Am Stat Assoc. 1987;81:366-74.
3. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011;30(4):377-99.

Appendix A. List of SAP Signatories

Name	Title	Role/Functional Area
[redacted]		Author
		Statistical Sciences
		Statistical Sciences
		Statistical Programming
		Medical Monitor

Appendix B. Definition of Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) will be identified using the following search criteria (**Note:** for each database lock, the categories of AESIs will follow the latest version of Product Safety Statistical Analysis Plan for Upadacitinib, with the exceptions of Hepatitis B Reactivation which is not an AESI. AESIs with the corresponding code for the current MedDRA version in that DBL will be shown in a summary table):

AESI	Type of MedDRA Query	Broad or Narrow Search	SMQ/CMQ Search Criteria
Serious Infections	CMQ		"Infections" – Subset for SAEs
Opportunistic Infection excluding tuberculosis and herpes zoster	CMQ		"Opportunistic Infection excluding tuberculosis and herpes zoster"
Possible malignancy	SMQ	Narrow	"Malignancies"
Malignancy	SMQ	Narrow	"Malignant Tumours"
Non-Melanoma Skin Cancer (NMSC)	SMQ/CMQ	SMQ Narrow	Skin Malignant Tumours (Narrow SMQ) removing Melanoma CMQ
Malignancy excluding NMSC			Malignancy Tumours Narrow SMQ and removing NMSC output
Lymphoma	SMQ	Broad	"Malignant Lymphomas"
Hepatic Disorder	SMQ	Narrow	"Drug Related Hepatic Disorders"
Adjudicated Gastrointestinal Perforations	Medical review of events identified by the "Gastrointestinal Perforation" SMQ Narrow search		
Anemia	CMQ		"Non-Hemolytic and Non-Aplastic Anemias"
Neutropenia	CMQ		"Hematological Toxicity – Neutropenia"
Lymphopenia	CMQ		"Hematological Toxicity – Lymphopenia (Upadacitinib Product Specific)"
Herpes Zoster	CMQ		"Herpes Zoster"
Renal Dysfunction	SMQ	Narrow	"Acute Renal Failure"

AESI	Type of MedDRA Query	Broad or Narrow Search	SMQ/CMQ Search Criteria
Active Tuberculosis	CMQ		"Active Tuberculosis"
Adjudicated cardiovascular events[a]	Output from CAC		
MACE*			
Cardiovascular Death			
Non-fatal Myocardial Infarction			
Non-fatal Stroke			
Other Adjudicated Cardiovascular Events			
Undetermined/Unknown Cause of Deaths			
Adjudicated Thrombotic Events	Output from CAC		
VTE**			
Deep Vein Thrombosis			
Pulmonary Embolism			
Other Venous Thrombosis			
Arterial Thromboembolic Events (non-cardiac, non-neurologic)			

CAC Cardiovascular Adjudication Committee; CMQ company MedDRA query; PT preferred term; SMQ standard MedDRA query

* MACE: Major Adverse Cardiovascular Events, defined as cardiovascular death, non fatal myocardial infarction and non fatal stroke.

** VTE: Venous thromboembolic events, defined as deep vein thrombosis (DVT) and pulmonary embolism (PE) (fatal and non fatal).

a. Reviewed and adjudicated by an independent Cardiovascular Adjudication Committee in a blinded manner.

Appendix C. Rescue Definition

The topical medications for AD therapy are coded to the following drug classes. Among these AD medications, the potential AD rescue medications are determined through a medical review process.

1. Plain Topical Corticosteroids
2. High Potency Topical Corticosteroids
3. Medium Potency Topical Corticosteroids
4. Low Potency Topical Corticosteroids
5. Topical Calcineurin Inhibitor Therapy
6. Other Topical therapy (not including moisturizers/emollients)

Concomitant medications that are categorized as "potential AD rescue" per medical review AND in categories 1 - 6 above are considered as rescue medications in Period 1 and Period 2.

The medical review process is documented in the Rescue Medication Medical Review Process - Upadacitinib AD.

Appendix D. Potentially Clinically Important Criteria for Safety Endpoints

The criteria for Potentially Clinically Important (PCI) laboratory findings are described in Table D-1 and Table D-2, PCI criteria for the liver function tests are described in Table D-3, and the PCI criteria for vital sign findings are described in Table D-4.

Table D-1. Criteria for Potentially Clinically Important Hematology Values

		Definition of Potentially Clinically Important
Hematology Variables	**Units**	**Very Low**
Hemoglobin	g/dL	< 8.0
Platelets count	10^9/L	< 50.0
WBC count	10^9/L	< 2.0
Neutrophils	10^9/L	< 1.0
Lymphocytes	10^9/L	< 0.5

Table D-2. Criteria for Potentially Clinically Important Chemistry Values

		Definition of Potentially Clinically Important	
Chemistry Variables	**Units**	**Very Low**	**Very High**
ALP	U/L		> 5.0 × ULN
SGOT/AST	U/L		> 5.0 × ULN
SGPT/ALT	U/L		> 5.0 × ULN
Albumin	g/L	< 20	
Glucose	mmol/L	< 2.2	> 13.9
Triglycerides	mmol/L		> 5.7
Creatinine	mcmol/L		> 3.0 × ULN
Potassium	mmol/L	< 3.0	> 6.0
Calcium	mmol/L	< 1.75	> 3.1
Sodium	mmol/L	< 130	> 155
Phosphate	mmol/L	< 0.6	
CPK	U/L		> 5.0 × ULN
Total Cholesterol	mmol/L		> 10.34

Table D-3. Criteria for Potentially Clinically Important Liver Function Tests

		Definition of Potentially Clinically Important
Variables	**Units**	**Very High**
AST	U/L	≥ 3 × ULN ≥ 5 × ULN ≥ 10 × ULN ≥ 20 × ULN
ALT	U/L	≥ 3 × ULN ≥ 5 × ULN ≥ 10 × ULN ≥ 20 × ULN
Total Bilirubin	UMOL/L	≥ 2 × ULN
Alkaline phosphatase	U/L	≥ 1.5 × ULN
ALT (U/L) and/or AST (U/L) and concurrent TBL (UMOL/L)		ALT and/or AST ≥ 3 × ULN and concurrent TBL ≥ 1.5 × ULN ALT and/or AST ≥ 3 × ULN and concurrent TBL ≥ 2 × ULN

Table D-4. Criteria for Potentially Clinically Important Vital Sign Values

Vital Sign	Category	Criteria for Potential Clinically Significant Vital Signs
Systolic blood pressure	Low	Value ≤ 90 mmHg and decrease ≥ 20 mmHg from Baseline
	High	Value ≥ 160 mmHg and increase ≥ 20 mmHg from Baseline
Diastolic blood pressure	Low	Value ≤ 50 mmHg and decrease ≥ 10 mmHg from Baseline
	High	Value ≥ 100 mmHg and increase ≥ 10 mmHg from Baseline
Pulse	Low	Value ≤ 50 bpm and decrease ≥ 15 bpm from Baseline
	High	Value ≥ 120 bpm and increase ≥ 15 bpm from Baseline
Weight (adults)	High	> 7% increase from Baseline
	Low	> 7% decrease from Baseline
Weight (Adolescents)	Low	> 7% decrease from Baseline

Appendix E. National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) for Selected Lipid Parameters

- LDL cholesterol (< 3.36, ≥ 3.36 and < 4.14, ≥ 4.14 mmol/L)
- HDL cholesterol (< 1.03, ≥ 1.03 mmol/L)
- Total cholesterol (< 5.17, ≥ 5.17 and < 6.21, ≥ 6.21 mmol/L)
- Triglycerides (< 1.69, ≥ 1.69 and < 2.26, ≥ 2.26 mmol/L)