Statistical Analysis Plan for Study M21-324

Glabellar Lines: Safety and Efficacy and OnabotulinumtoxinA X in Subjects with Glabellar Lines

Date: 02 August 2022

Version 3.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for OnabotA X Study M21-324 Glabellar Lines: Safety and Efficacy of OnabotulinumtoxinA X in Subjects with Glabellar Lines.

Study M21-324 examines the efficacy and safety of OnabotA X in female subjects with severe glabellar lines.

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 Linux operating system.

2.0 Study Design and Objectives

2.1 Objectives, Hypotheses and Estimands

The primary objective of the study is to evaluate the safety of OnabotA X injection in the glabellar region of female subjects with severe GL.

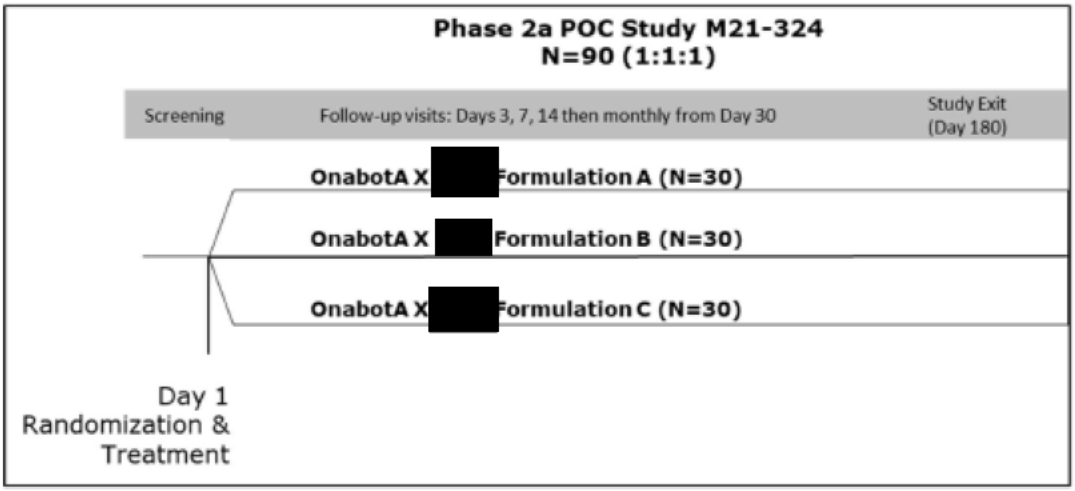
The clinical hypothesis is that OnabotA X has an acceptable safety profile when administered to the corrugator and procerus muscles in subjects with severe GL.

No estimand is defined for the safety evaluations.

2.2 Study Design Overview

The schematic of the study is shown in Figure 1.

Figure 1. Study Schematic



2.3 Treatment Assignment and Blinding

Subjects will be randomized to Formulation A, Formulation B, or Formulation C, each in combination with standard of care, in a 1:1:1 ratio. AbbVie will provide instructions for OnabotA X Formulations A, B, and C admixture preparations and treatment administration separately, in the pharmacy manual.

2.4 Sample Size Determination

A sample size of 90 (30 per treatment group) subjects will provide sufficient data for safety evaluations of OnabotA X to support future placebo-controlled studies in larger sample sizes, powered for efficacy evaluations.

3.0 Endpoints

3.1 Primary Endpoint(s)

Not applicable.

3.2 Secondary Endpoint(s)

Not applicable.

3.3 Other Efficacy Endpoint(s)

All efficacy endpoints will utilize the Facial Wrinkle Scale for Glabellar Lines (FWS-GL) and/or the Allergan Glabellar Line Severity Scale (AGLSS), each of which are scored on a 0-3 range, where 0 = None, 1 = Mild, 2 = Moderate, and 3 = Severe.

The efficacy endpoints for the investigator-rated and subject-rated FWS-GL at maximum frown include:

- Number and proportion of subjects who achieve 1-grade improvement from baseline;
- Number and proportion of subjects who achieve 2-grade improvement from baseline;
- Number and proportion of subjects who achieve 2-grade improvement from baseline in both Investigator and Subject ratings;
- Number and proportion of subjects who achieve a "None" or "Mild" rating

With the exception of the endpoint above that is based on both the Investigator and Subject ratings, the other endpoints listed above are calculated separately for Investigator-rated and subject-rated FWS-GL.

The efficacy endpoints for the Allergan Glabellar Line Severity Scale (AGLSS) at maximum frown evaluated by independent investigator (separate from the investigator evaluating FWS-GL) include:

- Number and proportion of subjects rated at least "Mild" at baseline who achieve 1-grade improvement from baseline;
- Number and proportion of subjects rated at least "Moderate" at baseline who achieve 2-grade improvement from baseline;

- Number and proportion of subjects at least "Moderate" at baseline who achieve a "None" or "Mild" rating

The efficacy endpoints for the subjects whose glabellar lines were rated at least "Mild" at baseline at rest include:

- Number and proportion of subjects with 1-grade improvement from baseline in investigator-rated FWS-GL;
- Number and proportion of subjects with 1-grade improvement from baseline in FWS- subject-rated GL;
- Number and proportion of subjects who achieve a 1-grade improvement from baseline in AGLSS

The FWS-GL endpoints will be assessed at screening, baseline, and at each follow-up visit, while the AGLSS endpoints will only be assessed at baseline and Day 30.

3.4 Safety Endpoint(s)

The safety endpoints for this study include:

- Adverse Events
- Abbreviated Physical Examination (general appearance, head, ears, eyes, nose, throat, and neck)
- Clinical Laboratory Test (hematology, chemistry, and urinalysis)
- Vital Sign Measurements (body temperature, pulse rate, respiration rate, systolic and diastolic blood pressure)
- Electrocardiogram (heart rate, QRS duration, QT interval, QTcB interval, QTcF interval, ST segment, RR interval, PR interval)
- Neurologic Assessment

3.5 Additional Endpoint(s)

The following additional endpoints will also be assessed:

Immunogenicity: Blood samples for immunogenicity testing will be collected from all subjects treated with OnabotA X at Day 1 (Baseline), Day 30, Day 90, and End-of-Study (Day 180). Collected samples will be processed to yield serum for detection of binding and neutralizing antibodies to OnabotulinumtoxinA.

Hypersensitivity: Blood samples are to be collected within 2 hours of suspected anaphylaxis or systemic hypersensitivity reaction.

4.0 Analysis Populations

The following population sets will be used for the analyses.

The Full Analysis Set (FAS) includes all randomized subjects who received at least 1 dose of study drug. The FAS will be used for all efficacy and baseline analyses. Subjects in this population will be analyzed per randomization, regardless of actual treatment received.

The Safety Analysis Set consists of all subjects who received at least 1 dose of study drug. The Safety Analysis Set will be used for all safety analyses. Due to the difficulty of determining the actual treatment received if wrong kits are given or reconstitution is not done correctly, subjects in this population will be analyzed per randomization.

5.0 Subject Disposition

The total number of subjects who were screened, enrolled, and treated will be summarized. Reasons for exclusion, including screen failure, will be summarized.

A summary of subject accountability will be provided where the number of subjects in each of the following categories will be summarized for each treatment group:

- Subjects enrolled (randomized) in the study;
- Subjects who were treated;
- Subjects who completed the study;
- Subjects who prematurely discontinued (all reasons and primary reason);

- Subjects in each analysis population, as applicable.

For end of study participation, the number and percentage of subjects who completed the protocol defined follow-up period (or did not with associated reasons) will be summarized overall and by treatment group.

6.0 Study Drug Duration and Compliance

Duration of exposure will be summarized with descriptive statistics (mean and standard deviation, median, Q1, Q3, minimum, and maximum). The number of subjects exposed for specific period of time (1-30 days, 31-60 days, 61-90 days, 91-120 days, 121-150 days, 151-180 days, and >180 days) will also be summarized. Duration of exposure will be calculated as date of study exit minus date of study drug administration +1.

7.0 Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

Demographics, baseline characteristics, medical history, prior and concomitant medications, and concurrent procedure will be summarized overall and by treatment group for the FAS. Categorical variables will be summarized with the number and percentage of subjects; percentages will be calculated based on the number of non-missing observations. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum, and maximum).

7.1 Demographics and Baseline Characteristics

Continuous demographic variables include age. Categorical demographic variables include sex, ethnicity, race, age group (18-25, 26-40, 41-55, 56-64, or ≥ 65 years).

Baseline characteristics include weight, height, body mass index (BMI), Fitzpatrick skin type, baseline Investigator-rated and subject-rated FWS-GL severity at maximum frown and rest, and baseline AGLSS severity at maximum frown and at rest.

7.2 Medical History

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 and preferred term) will be summarized overall and by treatment group. The system organ class (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).

7.3 Prior and Concomitant Medications

Prior and concomitant medications will be summarized by generic name. A prior medication is defined as any medication taken prior to the date of the first dose of study drug. A concomitant medication is defined as any medication that started prior to the date of study drug administration and continued to be taken after the first dose of study drug or any medication that started on or after the date of the first dose of study drug. 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.

7.4 Concurrent Procedure

All procedures undergone on or after Study Day 1 visit through the exit visit will be considered concurrent procedures. Concurrent procedure will be summarized by MedDRA high-level term and preferred term. The MedDRA high level term will be presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each high-level term. A listing will be generated for concurrent procedures.

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

Not applicable.

9.0 Efficacy Analyses

9.1 General Considerations

Data will be summarized for subjects for the FAS Population. For the efficacy analyses, subjects are summarized based on the randomized treatment assigned.

The number and percentage (or proportion) of the subjects who are responders will be summarized. Calculation of a 95% CI with an exact method based on the binomial distribution will be utilized alongside the summary data.

"Baseline" refers to the last non-missing observation before the first administration of study drug or randomization if no study drug is given.

9.2 Handling of Missing Data

Missing data will not be imputed. Instead, the following method will be used for the efficacy summary data:

- As Observed (AO): The AO analysis will not impute values for missing evaluations, and thus a subject who does not have an evaluation on a scheduled visit (within the applicable visit window) will be excluded from the AO analysis for that visit. AO will include all values collected in the study.

9.3 Primary Efficacy Endpoint(s) and Analyses

9.3.1 Primary Efficacy Endpoint(s)

Not applicable.

9.3.2 Main Analysis of Primary Efficacy Endpoint(s)

Not applicable.

9.3.3 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoint(s)

Not applicable.

9.4 Secondary Efficacy Endpoints and Analyses

9.4.1 Key Secondary Efficacy Endpoints

Not applicable.

9.4.2 Main Analyses of Key Secondary Efficacy Endpoints

Not applicable.

9.4.3 Sensitivity and Supplementary Analyses for Key Secondary Efficacy Endpoints

Not applicable.

9.4.4 Supportive Secondary Efficacy Endpoints and Analyses

Not applicable.

9.5 Additional Efficacy Analyses

Additional Efficacy Endpoints are:

- Achievement of ≥1-grade improvement from baseline on the investigator-rated FWS-GL at maximum frown by visit
- Achievement of ≥1-grade improvement from baseline on the subject-rated FWS-GL at maximum frown by visit
- Achievement of ≥2-grade improvement from baseline on the investigator-rated FWS-GL at maximum frown by visit
- Achievement of ≥2-grade improvement from baseline on the subject-rated FWS-GL at maximum frown by visit

- Achievement of None or Mild on the investigator-rated FWS-GL at maximum frown by visit
- Achievement of None or Mild on the subject-rated FWS-GL at maximum frown by visit
- Achievement of ≥2-grade improvement from baseline on both the investigator-rated and subject-rated FWS-GL at maximum frown by visit
- Achievement of ≥1-grade improvement from baseline on the AGLSS at maximum frown for those who were rated at least Mild at baseline
- Achievement of ≥2-grade improvement from baseline on the AGLSS at maximum frown for those who were rated at least Moderate at baseline
- Achievement of None or Mild on the AGLSS at maximum frown for those who were rated at least Moderate at baseline
- Achievement of ≥1-grade improvement from baseline on the investigator-rated FWS-GL at rest by visit for those who were rated at least Mild at baseline
- Achievement of ≥1-grade improvement from baseline on the subject-rated FWS-GL at rest by visit for those who were rated at least Mild at baseline
- Achievement of ≥1-grade improvement from baseline on the AGLSS at rest for those who were rated at least Mild at baseline

Listings of all endpoint values for each subject will also be provided.

9.6 Efficacy Subgroup Analyses

Not applicable.

10.0 Safety Analyses

10.1 General Considerations

Safety data will be summarized for the Safety Analysis Set. For the safety analyses, subjects are summarized based on the treatment as randomized.

For safety analyses, "Baseline" refers to the last non-missing observation before the first administration of study drug unless otherwise noted.

10.2 Adverse Events

Adverse events (AEs) will be summarized overall and by treatment group and presented using primary MedDRA System Organ Classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the AE tables and in the clinical study report. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

10.2.1 Treatment-Emergent Adverse Events

Treatment-emergent AEs are defined as any AE with the onset that is after the study drug administration. Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent. All treatment-emergent AEs 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.

10.2.2 Adverse Event Overview

An overview of AEs will be presented consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- Any treatment-emergent AE
- Any treatment-emergent AE related to study treatment according to the investigator
    - Any treatment-emergent AE related to study procedure according to the investigator
    - Any treatment-emergent AE related to study drug according to the investigator
- Any severe treatment-emergent AE

- Any severe treatment-emergent AE related to study treatment according to the investigator
- Any serious treatment-emergent AE
  - Any serious treatment-emergent AE related to study treatment according to the investigator
- Any treatment-emergent AE leading to death
- Any treatment-emergent PDSOT AEs
- All deaths

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

Treatment-emergent adverse events will be summarized by SOC and PT; by maximum severity and SOC and PT; and by subject number and SOC and PT. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

In addition, treatment-emergent adverse events will be summarized by PT and sorted by decreasing frequency for the overall group. Treatment-related treatment-emergent adverse events, study drug related treatment-emergent adverse events, and study procedure related treatment-emergent adverse events will also be summarized by SOC and PT.

10.2.4 SAEs (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

SAEs (including deaths) will be summarized by SOC and PT and in listing format.

10.2.5 Potential Distant Spread of Toxin Adverse Events

To assess PDSOT, MedDRA preferred terms that may be associated with botulinum toxin effects have been identified (Appendix B). All TEAEs associated with PDSOT will be tabulated by PT; in addition, all PDSOT TEAEs will be listed by subject.

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 before the first dose of study drug will be excluded. The clinical laboratory tests defined in the protocol operations manual (e.g., hematology, clinical chemistry, and urinalysis) will be summarized by treatment group.

Each laboratory 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 will be summarized for selected laboratory variables, 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.

Changes in laboratory parameters will be tabulated using shift tables categorized as low, normal, or high based on the normal ranges of the laboratory used for each sample. A shift table from baseline to the minimum post-baseline value, to the maximum post-baseline value, and to the final post-baseline value will be created.

Laboratory abnormalities will be evaluated based on Potentially Clinically Important (PCI) criteria (Table C-1 in Appendix C). For each laboratory PCI criterion, the number and percentage of subjects who have a post-baseline laboratory value meeting the criteria will be summarized. The percentages will be calculated relative to the number of participants with at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCI postbaseline value during the study that is more extreme than baseline (if present).

Listings will be provided to summarize subject-level laboratory data for subjects meeting PCI criteria.

A listing of possible Hy's Law cases, defined as those who meet all of the following conditions simultaneously, will be provided: ALT > 3 × ULN or AST > 3 × ULN that is associated with an increase in bilirubin ≥ 2 × ULN and alkaline phosphatase < 2 × ULN.

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 by treatment group.

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 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.

Vital sign variables will be evaluated based on PCI criteria (Table C-2 in Appendix C). For each vital sign PCI criterion, the number and percentage of subjects who have a vital sign value meeting the criteria will be summarized. Except for temperature, the percentages will be calculated relative to the number of participants with an available baseline value and at least 1 post-baseline assessment; the numerator will be the total number of participants with at least 1 PCI post-baseline value during the study that is more extreme than baseline. For temperature, the percentages will be calculated based on the number of participants with at least 1 post-baseline assessment. The numerator will be the total number of participants with at least 1 PCI post-baseline value during the study; no baseline is required, however if a baseline value is present the observed value must also be more extreme than baseline to be considered PCI.

Listings will be provided to summarize subject-level vital sign data for subjects meeting PCI criteria.

10.5 Safety Subgroup Analyses

Not applicable.

10.6 Other Safety Analyses

Electrocardiogram (ECG): Descriptive statistics for quantitative ECG parameters (i.e., heart rate, QRS duration, QT interval, QTc interval, QTcB interval, QTcF interval, RR interval and PR interval) at baseline, postbaseline, and changes from baseline values at each postbaseline timepoint will be presented.

ECG parameter values are considered PCI if ECG values meet either the actual value or change from baseline PCI high criteria listed in Table C-3 of Appendix C. The number and percentage of participants with PCI post-baseline values will be tabulated. The percentages will be calculated relative to the number of participants with at least 1 post-baseline assessment. The numerator will be the total number of participants with at least 1 PCI post-baseline value during the study that is more extreme than baseline (if present).

A supportive listing of participants with PCI post-baseline values will be provided.

[redacted]

11.0 Other Analyses

Immunogenicity: Immunogenicity results, manifested as the binding antibodies and neutralizing antibodies, will be summarized overall and by treatment group for each sampling timepoint. A listing of each subject's results by visit will also be produced.

Hypersensitivity: Blood sample results from hypersensitivity evaluations, if any are conducted, will also be listed.

12.0 Interim Analyses

Not applicable.

12.1 Data Monitoring Committee

Not applicable.

13.0 Overall Type-I Error Control

Not applicable.

14.0 Version History

Table 1. SAP Version History Summary

Version	Date of Approval	Summary
1.0	05 August 2021	Initial version
2.0	10 October 2021	In Section 10.6, added text about ECG because the protocol was amended (v3.0) to include collection of ECG. Includes ECG parameters, ECG PCI table, and text stating how the ECG parameters will be summarized and listed. Updated Section 10.2.2 and Section 10.2.3 regarding AE overview table, and added treatment-related adverse events tables. Updated Section 10.3 to add lab PCI. Updated Section 10.4 to revise the vital PCI language.
3.0		Section 4.0, changed the safety analysis set to be analyzed per randomization due to the difficulty of determine the actual treatment Section 7.1, changed age group from <65, or ≥ 65 years to 18-25, 26-40, 41-55, 56-64, or ≥ 65 years Table B-1: MedDRA preferred terms evaluated for PDSOT, removed the term “Extraocular muscles paresis”, added the term “Opthalmoplegia” Updated Table C-1 Criteria for Potentially Clinically Important Clinical Laboratory Values: updated the value corresponding to Cholesterol, Glucose, and Triglycerides. Changed “Inorganic phosphorus” to “Phosphate”

15.0 References

Appendix A. Protocol Deviations

The number and percentage of unique subjects reporting significant protocol deviations will be summarized in total and by treatment group for all randomized or treated subjects. The number and percentage of unique subjects with protocol deviation categories below will also be summarized in total and by treatment group.

- Subject entered into the study even though s/he did not satisfy entry criteria.
- Subject received wrong treatment or incorrect dose of study.
- Subject took prohibited concomitant medication or concurrent procedure.

Appendix B. Definition of Possible Distant Spread of Toxin

Table B-1. MedDRA Preferred Terms Evaluated for PDSOT

Accommodation disorder	Hyporeflexia
Aspiration	Hypotonia
Bell's Palsy	Ileus paralytic
Botulism	Muscular weakness
Bradycardia	Opthalmoplegia
Bulbar palsy	Paralysis
Constipation	Paresis cranial nerve
Cranial nerve palsies multiple	Pelvic floor muscle weakness
Cranial nerve paralysis	Peripheral nerve palsy
Diaphragmatic paralysis	Peripheral paralysis
Diplopia	Pneumonia aspiration
Dry mouth	Pupillary reflex impaired
Dysarthria	Respiratory arrest
Dysphagia	Respiratory depression
Dysphonia	Respiratory failure
Dyspnoea	Speech disorder
Eyelid function disorder	Urinary retention
Eyelid ptosis	Vision blurred
Facial paralysis	Vocal cord paralysis
Facial paresis	Vocal cord paresis

Note: Table is based on MedDRA 25.0; the actual list used for analysis will be based on the MedDRA version in use at the time of database lock.

Appendix C. Potentially Clinically Important Criteria for Safety Endpoints

Table C-1. Criteria for Potentially Clinically Important Clinical Laboratory Values

Parameter	Flag	Criteria[a] Observed Value
Hematology		
Hemoglobin (g/L)	High	Increase in >2 g/dL above ULN or > baseline if baseline >ULN
	Low	<100
WBC Count (10^9/L)	High	-
	Low	< 3
Neutrophils (10^9/L)	High	-
	Low	<1.5
Lymphocytes (10^9/L)	High	>4
	Low	<0.8
Platelets (10^9/L)	High	-
	Low	<75.0
International normalized ratio (INR)	High	>1.5 x ULN; >1.5 times above baseline if on anticoagulation
	Low	Not Applicable
Chemistry		
Albumin (g/L)	High	-
	Low	<30
Alkaline Phosphatase (U/L)	High	>2.5 x ULN
	Low	-
Alanine Aminotransferase (U/L)	High	>3.0 x ULN
	Low	-
Aspartate Aminotransferase (U/L)	High	>3.0 x ULN
	Low	-

Table C-1. Criteria for Potentially Clinically Important Clinical Laboratory Values (Continued)

Parameter	Flag	Criteria[a] Observed Value
Total Bilirubin (umol/L)	High	>1.5 x ULN
	Low	-
Calcium (mmol/L)	High	Corrected serum calcium >2.9@; Ionized calcium >1.5
	Low	Corrected serum calcium <2.0@; Ionized calcium <1.0
Cholesterol (mmol/L)	High	>10.34
	Low	-
Creatinine (umol/L)	High	>1.5 x ULN
	Low	-
Gamma Glutamyl Transferase (U/L)	High	>2.5 x ULN
	Low	-
Glucose (mmol/L)	High	>13.9
	Low	<2.2
Potassium (mmol/L)	High	>5.5
	Low	<LLN
Sodium (mmol/L)	High	>150
	Low	<130
Triglycerides (mmol/L)	High	>5.70
	Low	-
Phosphate (mmol/L)	High	-
	Low	<0.8

a. A post-baseline value must be more extreme than baseline (if present) to be considered a potentially clinically important finding.

@ Calcium corrected for Albumin (can be used if it is confirmed with the lab that the result has been corrected for Albumin and not a different protein).

Note: LLN = Lower Limit of Normal; ULN = Upper Limit of Normal

The criteria for PCI criteria for vital sign findings are described in Table C-2.

Table C-2. Criteria for Potentially Clinically Important Vital Sign Values

Parameter	Flag	Criteria[a]	
		Observed Value	Change from Baseline
Sitting systolic blood pressure, mm Hg	High	≥ 160	Increase of ≥ 20
	Low	≤ 90	Decrease of ≥ 20
Sitting diastolic blood pressure, mm Hg	High	≥ 100	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Sitting pulse rate, bpm	High	≥ 110	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Temperature, degrees C	High	≥ 38.3	-
	Low	-	-

bpm = beats per minute; C = Celsius

a. Except for temperature, a post-baseline value is considered potentially clinically important if it meets both the observed-value and the change-from-baseline criteria; for temperature, only the observed-value criterion is needed to be potentially clinically important (but must be more extreme than baseline if baseline is present).

The criteria for PCI criteria for ECG findings are described in Table C-3.

Table C-3. Criteria for Potentially Clinically Important ECG Values

Parameter	Unit	Criteria[a]	
		Observed Value	Change from Baseline
QRS interval	msec	≥ 150	-
PR interval	msec	≥ 250	-
QTcB	msec	> 500	Increase of > 60
QTcF	msec	> 500	Increase of > 60

QTcB = QT interval corrected for heart rate using the Bazett formula.

QTcF = QT interval corrected for heart rate using the Friderica formula.

a. A post-baseline value is considered potentially clinically important if it meets either the observed-value or the change-from-baseline criteria (but must be more extreme than baseline if baseline is present).