

Statistical Analysis Plan for Study M21-509

A Phase 3, Multicenter, Open-label Study to Evaluate the Safety of AGN-151586 for the Treatment of Glabellar Lines

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Version 4.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for AGN-151586 (Botulinum Neurotoxin Serotype E) Study M21-509 with protocol title “A Phase 3, Multicenter, Open-label Study to Evaluate the Safety of AGN-151586 for the Treatment of Glabellar Lines”.

Study M21-509 examines the safety of AGN-151586 in subjects with moderate to 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 UNIX operating system.

2.0 Study Design and Objectives

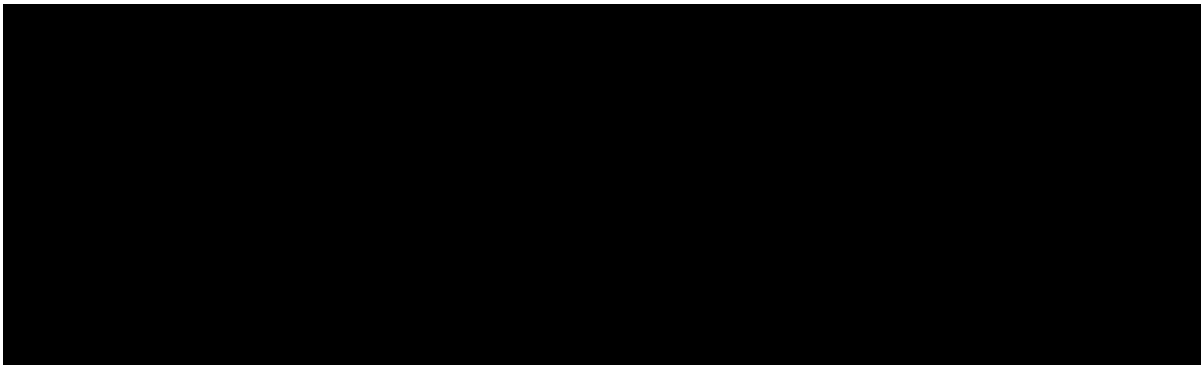
2.1 Objectives, Hypotheses and Estimands

The objective of the study is to evaluate the safety of AGN-151586 over multiple repeat treatments in subjects with moderate to severe GL over 18 weeks. The clinical hypothesis is that AGN-151586 at [REDACTED] has an acceptable safety profile after multiple repeat treatments of the study drug over the course of 18 weeks.

No hypothesis will be tested, and no estimands are provided.

2.2 Study Design Overview

The schematic of the study is shown in [Figure 1](#).



Enrolled subjects will receive the first treatment at Hour 0 on Day 1 (baseline). They may receive up to 2 retreatments in this study, based on meeting retreatment criteria at each retreatment reassessment, with a total of up to 3 treatments. No retreatment is allowed after the scheduled retreatment visit.

2.3 Treatment Assignment and Blinding

Subjects will be enrolled in the study and will receive unblinded AGN-151586 [REDACTED] at each treatment administration. There will be no randomization or stratification.

2.4 Sample Size Determination



No formal hypothesis testing will be performed.

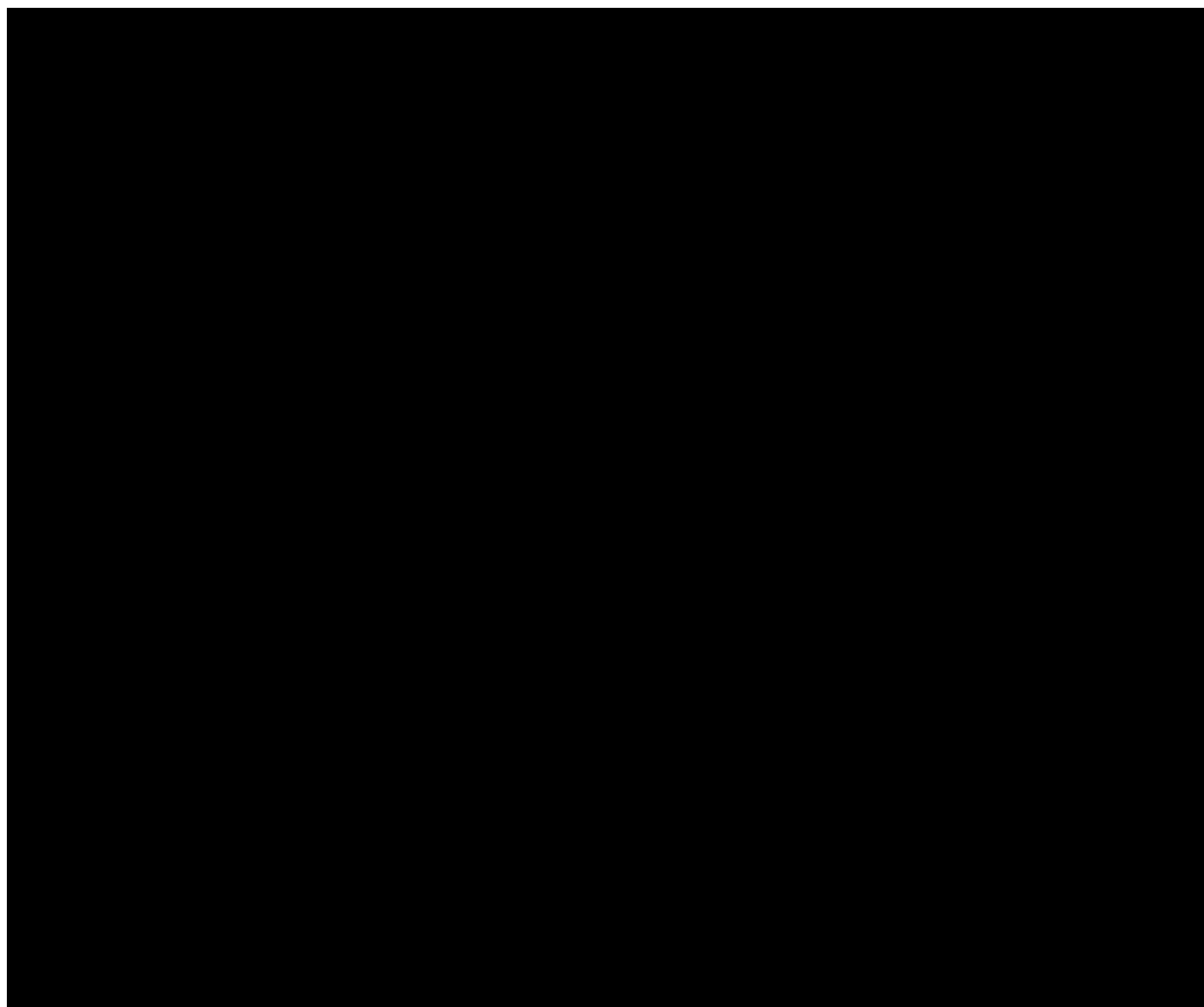
3.0 Endpoints

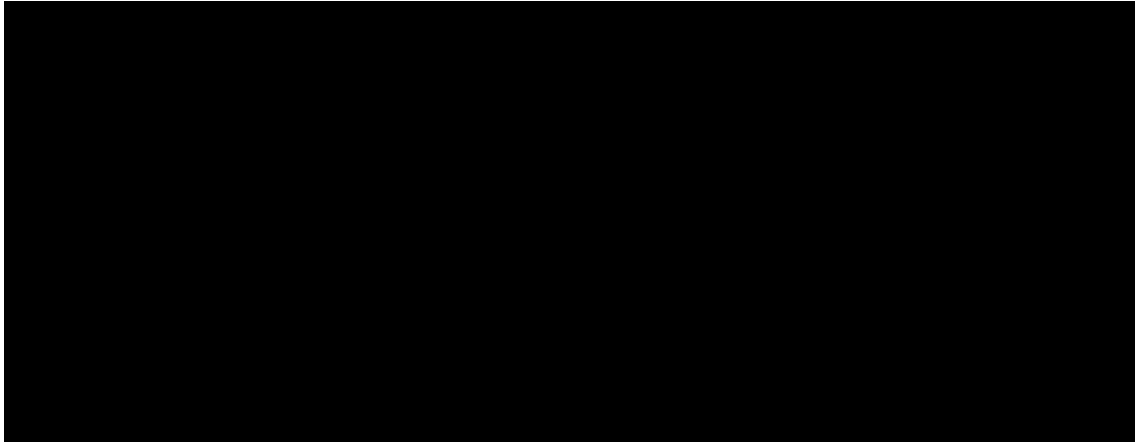
3.1 Primary Endpoints

The primary endpoints are incidence of adverse events, change from baseline in vital signs parameters, change from baseline in 12-lead electrocardiogram (ECG) parameters, and presence of binding and neutralizing antidrug antibodies.

3.2 Secondary Endpoint

Not applicable.





3.4 Safety Endpoints

The safety endpoints evaluated in this study are the primary endpoints discussed in Section 3.1. A neurological assessment (including examination of cranial nerves II through VII) will be evaluated as an additional safety measure. After the screening visit, neurological assessment abnormalities (or worsening of a baseline condition) will be captured as AEs.

3.5 Additional Endpoints

Not applicable.

4.0 Analysis Populations

The following population sets will be used for the analyses.

The Intent-to-Treat (ITT) Population includes all enrolled subjects and will be used for all baseline and efficacy analyses.

The Safety Analysis Set consists of all subjects who were treated with at least 1 dose of study drug (i.e., AGN-151586). The Safety Analysis Set will be used for all safety analyses.

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:

- Subjects enrolled in the study;
- Subjects treated with at least one dose of study drug;
- Subjects who completed protocol-specified treatment;
- Subjects who prematurely discontinued study drug;
- Subjects in each analysis population.

For end of study participation, the number and percentage of subjects who completed the protocol defined follow-up period will be summarized.

6.0 Study Drug Duration and Compliance

For the safety population, the number of subjects treated will be presented by treatment cycles (i.e., Day 1, retreatment 1, retreatment 2), any treatment, and number of treatments (i.e., 1 dose, 2 doses, 3 doses). If a subject does not receive the full dose, this will be indicated; significant deviations to dosing will be reported.

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

Demographics, baseline or disease characteristics, medical history, and prior and concomitant medications will be summarized for the ITT population overall. 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, weight, height, and body mass index (BMI). Categorical demographic and baseline characteristic variables include sex, ethnicity, race, prior aesthetic toxin use, Fitzpatrick skin type, FWS by investigator at maximum frown, FWS by subject at maximum frown, FWS by investigator at rest, and FWS by subject at rest.

7.2 Medical History and Prior and Concurrent Procedures

Medical history data will be reported and summarized separately from prior procedures data for the ITT population. Medical history data and prior procedure 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. 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). Similarly, the number and percentage of subjects in each prior procedure's category will be summarized using the MedDRA high level term and preferred term.

In addition, any concurrent procedures, defined as any procedure performed on or after the date of first treatment, will be summarized by MedDRA high level term and preferred term for the ITT population.

7.3 Prior and Concomitant Medications

Prior and concomitant medications will be summarized by generic name for the ITT population. 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 the first dose of study drug 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, but not after the date of the last visit assessment. 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.

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

The primary endpoints are safety endpoints and will be based on the Safety Analysis Set. No additional methods will be used to address potential intercurrent events, as all subjects who were treated will be included in the Safety Analysis Set with events reported as observed.

9.0 Efficacy Analyses

9.1 General Considerations

All efficacy analyses will be conducted in the ITT Population in each period. No statistical testing will be performed.

The Primary Analysis will be performed after all ongoing subjects have completed the study and the database has been locked. This will be the only and final analysis for the efficacy endpoints.

For efficacy analyses of FWS assessments, "baseline" refers to the last non-missing observation before either the first administration of study drug or enrollment date (i.e., Day 1) if no study drug is given or the administration of study drug during retreatment. The change from baseline values will be computed as the post-baseline value minus the baseline value.

9.2 Handling of Missing Data

Missing data will not be imputed for the efficacy analyses.

Data will be presented as observed (AO). The AO analysis will not impute values for missing evaluations, and thus a subject who does not have an evaluation for a scheduled visit will be excluded from the AO analysis for that visit. AO will include all values collected in the study.

9.3 Primary Efficacy Endpoint and Analyses

9.3.1 Primary Efficacy Endpoint

Not applicable.

9.3.2 Main Analysis of Primary Efficacy Endpoint

Not applicable.

9.3.3 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoint

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 Endpoints and Analyses

The assessments of the severity of GL at maximum frown using the validated FWS is based on the following scale for both investigator and subject:

- 0 = None
- 1 = Mild
- 2 = Moderate
- 3 = Severe

Analyses for additional efficacy endpoints will be performed on the ITT population using data as observed. The additional efficacy endpoints are listed in [Section 3.3](#).

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. Safety summaries will be presented by overall study and by study treatment cycle, as well as by number of doses received.

The safety parameters will include AEs, vital signs, 12-lead ECGs, neurological assessment (including examination of cranial nerves II through IV), and presence of binding and neutralizing antidrug antibodies. For each safety parameter evaluating change from baseline, the last non-missing safety assessment before study drug administration will be used as the baseline for all analyses of that parameter.

10.2 Adverse Events

Adverse events (AEs) will be summarized 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 per treatment cycle (based on AE start date) for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject during a treatment cycle, the highest severity and level of relationship to investigational product will be reported.

10.2.1 Treatment-Emergent Adverse Events

Treatment-emergent AEs (TEAEs) are defined as any AE with the onset that is after the first dose of study drug. Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent, unless known to have started prior to study treatment administration. All TEAEs will be summarized overall, as well as by primary MedDRA SOC and PT. The SOC's 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 treatment-emergent AEs will be summarized.

In addition, for both possible distant spread of toxin (PDSOT) TEAEs and treatment-related TEAEs, onset after study drug administration and duration will be evaluated. TEAE onset will be reported by number of days subsequent to the study drug administration and will be summarized with descriptive statistics. TEAE duration will be defined as ((end date minus start date) + 1 day) and will be summarized with descriptive statistics.

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 TEAE

- Any related TEAE
 - Any TEAE related to study drug according to the investigator
 - Any TEAE related to study procedure according to the investigator
- Any mild TEAE
 - Any mild TEAE related to study treatment according to the investigator
- Any moderate TEAE
 - Any moderate TEAE related to study treatment according to the investigator
- Any severe TEAE
 - Any severe TEAE related to study treatment according to the investigator
- Any serious TEAE
 - Any serious TEAE related to study treatment according to the investigator
- Any TEAE leading to study drug discontinuation
- Any TEAE leading to death
- Any PDSOT TEAE
- Any neurological assessment associated TEAE
- All deaths

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

TEAEs will be summarized by SOC and PT; by maximum relationship to study drug as assessed by the investigator (i.e., reasonable possibility) by SOC and PT; by maximum severity by SOC and PT; and listed by subject number by 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 adverse event will be counted only once per treatment cycle and the highest severity and level of relationship to study drug will be reported.

In addition, TEAEs will be summarized by PT and sorted by decreasing frequency. Frequent TEAE incidence will be reported for PTs with $\geq 5\%$ subject incidence, listed by SOC and PT.

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

Not applicable.

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

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

10.2.6 Possible Distant Spread of Toxin Adverse Events

PDSOT TEAEs will be summarized by PT. The PTs are identified in [Appendix B](#) and will be based on the current MedDRA version prior to database lock.

Tabular listings of PDSOT TEAEs will be provided.

10.2.7 Neurological Assessment Associated Adverse Events

The neurological assessment, which is comprised of a Focused Symptoms Questionnaire and a Focused Neurological Examination, will be conducted at selected study visits per protocol.

Neurological assessment associated TEAEs will be summarized by PT. The PTs will be based on the current MedDRA version prior to database lock.

Tables and listings of neurological assessment associated TEAEs will be provided.

10.3 Analysis of Laboratory Data

Not applicable.

10.4 Analysis of Vital Signs

Vital sign measurements of systolic and diastolic blood pressure, pulse rate, and temperature, and changes from baseline at each assessment timepoint will be summarized. In addition, potentially clinically important (PCI) vital sign values will be summarized.

Each vital sign parameter 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 parameter, 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.

Vital sign parameters will be evaluated based on PCI criteria (Table C-1 in [Appendix C](#)). For each vital sign PCI criterion, the number and percentage of subjects who have a vital sign value meeting the criterion will be summarized. Except for temperature, the percentages will be calculated relative to the number of subjects with an available baseline value and at least 1 post-baseline assessment; the numerator will be the total number of subjects 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 subjects with at least 1 post-baseline assessment. The numerator will be the total number of subjects 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, post-baseline, and changes from baseline values at each post-baseline 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-2 of [Appendix C](#). The number and percentage of subjects with PCI post-baseline values will be tabulated. The percentages will be calculated relative to the number of subjects with at least 1 post-baseline assessment. The numerator will be the total number of subjects with at least 1 PCI post-baseline value during the study that is more extreme than baseline (if present).

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

Neurologic Assessment: The neurologic assessment, which is comprised of a Focused Symptoms Questionnaire and a Focused Neurological Examination, will be conducted at selected study visits per protocol. Tables and listings of AEs related to the neurological assessment will be provided.

Immunogenicity Assessment: Immunogenicity results, manifested as the presence of binding antibodies (positive) and neutralizing antibodies (positive) to AGN-151586, will be summarized in a table for baseline, post-baseline, as well as at any time.

Immunogenicity findings (positive) will be tabulated with the number and percentage of subjects at each visit. Percentages will be based on the number of treated subjects with interpretable antibody assays at the specified visit.

11.0 Other Analyses

Not applicable.

12.0 Interim Analyses

No interim analysis is planned.

12.1 Data Monitoring Committee

No data monitoring committee (DMC) will be used for this study.

13.0 Overall Type-I Error Control

There is no formal hypothesis testing to be performed for this study. Data will be presented as observed.

14.0 Version History

Table 1. SAP Version History Summary

Version	Date	Summary
1.0	20 May 2021	Original version
2.0	21 December 2021	Updated study design, study visits and duration Added safety assessments for neurological assessment, ECG assessments Updated sample sizes, removed interim analysis Added PCI criteria for vital signs and ECG
3.0	09 November 2022	Added efficacy endpoint analyses of FWS at rest Clarified data collection at scheduled visits, not necessarily every visit Added TEAE onset and duration analyses Updated PDSOT terms
4.0	20 July 2023	Updated sample size section based on current protocol Clarified that prior procedures and concurrent procedures will be reported using MedDRA high level term and preferred term Added other efficacy endpoints Clarified that adverse events will be reported per treatment cycle based on AE start date Added mild TEAE and moderate TEAE descriptive summaries for the Adverse Event Overview Clarified that neurological assessment associated TEAEs would be reported

15.0 References

Not applicable.

Appendix A. Protocol Deviations

The number and percentage of subjects who reported at least one of the following protocol deviation categories will be provided.

- Subject entered into the study even though s/he did not satisfy entry criteria.
- Subject developed withdrawal criteria during the study and was not withdrawn.
- Subject received wrong treatment or incorrect dose of study treatment.
- Subject took prohibited concomitant medication.

Appendix B. Possible Distant Spread of Toxin

Preferred Terms Evaluated for PDSOT

Accommodation disorder	Hyporeflexia
Aspiration	Hypotonia
Bell's Palsy	Ileus paralytic
Botulism	Muscular weakness
Bradycardia	Ophthalmoplegia
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 version 25.1; the actual terms 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

The PCI criteria for vital sign findings are described in Table C-1.

Table C-1. 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 PCI criteria for ECG findings are described in Table C-2.

Table C-2. 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 Fridericia 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).