**Protocol C3651012**

# A PHASE 1, OPEN-LABEL, SINGLE DOSE STUDY TO INVESTIGATE THE PHARMACOKINETICS, PHARMACODYNAMICS, SAFETY, AND TOLERABILITY OF PONSEGROMAB ADMINISTERED SUBCUTANEOUSLY IN HEALTHY ADULT CHINESE PARTICIPANTS

**Statistical Analysis Plan**
**(SAP)**

**Version:** 1

**Date:** 18 May 2022

[redacted]

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## APPENDICES

# 1. VERSION HISTORY

**Table 1. Summary of Changes**

| Version/ Date | Associated Protocol Amendment | Rationale | Specific Changes |
|---|---|---|---|
| 1 18 May 2022 | Original 22 Apr 2022 | N/A | N/A |

# 2. INTRODUCTION

The purpose of this study is to evaluate the pharmacokinetics (PK), CCI safety, and tolerability of ponsegromab following 100 mg and 400 mg single subcutaneous (SC) dose in healthy adult Chinese participants. Results from this study will be used to inform clinical development of ponsegromab in China, to facilitate China's participation in global pivotal studies, and to support China registration of ponsegromab.

This statistical analysis plan (SAP) provides the detailed methodology for summaries and statistical analyses of the data to be collected in Study C3651012. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definitions or their analyses will also be reflected in a protocol amendment.

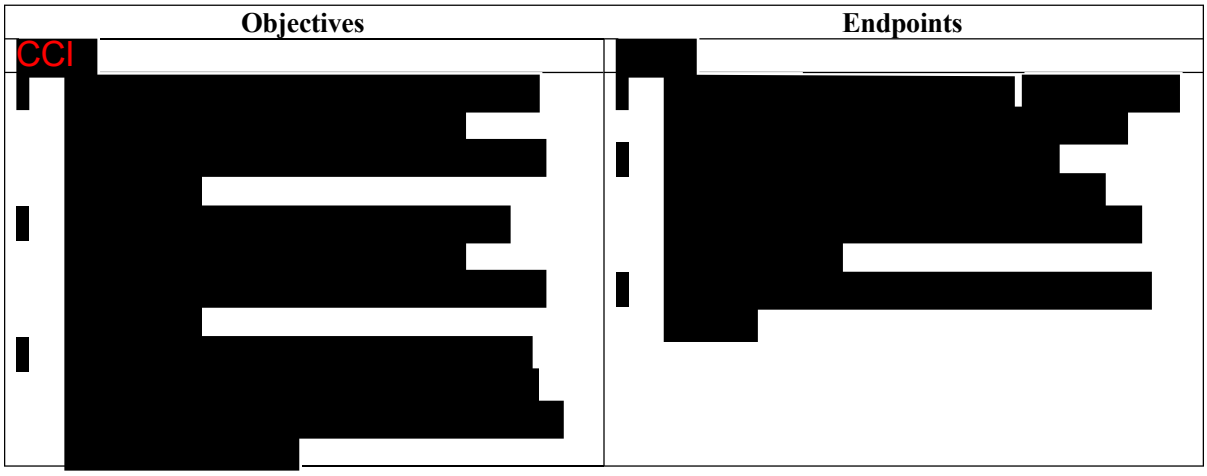
## 2.1. Modifications to the Analysis Plan Described in the Protocol

Not applicable.

## 2.2. Study Objectives, Endpoints, and Estimands

There are no estimands for this study.

| Objectives | Endpoints |
|---|---|
| **Primary:** | **Primary:** |
| • To characterize the serum PK of ponsegromab following a single SC administered dose in healthy adult Chinese participants. | • Ponsegromab serum PK parameters (unbound and total), as data permit: $AUC_{inf}$, $AUC_{last}$, $C_{max}$, $T_{max}$, and $t_{½}$. |
| **Secondary:** | **Secondary:** |
| • To evaluate the safety and tolerability of ponsegromab following a single SC administered dose in healthy adult Chinese participants. | • Adverse events (AE), clinical safety laboratory tests, vital signs (blood pressure, pulse rate), physical examinations, and 12-lead ECGs for approximately 18 weeks post single dose. |




### 2.3. Study Design

This is an open-label, single dose study to characterize the PK, CCI safety, and tolerability of ponsegromab following 100 mg or 400 mg single SC dose in healthy adult Chinese participants.

The study will enroll 2 cohorts of approximately 18 healthy adult Chinese participants (N=9 for each cohort).

Participants who meet eligibility criteria at baseline will receive a single SC dose of ponsegromab at 100 mg (Cohort 1) or 400 mg (Cohort 2) on Day 1. Participants in the 100 mg cohort will be dosed firstly, and will be kept under safety monitoring for 8 days at the clinical research unit (CRU). Progression to 400 mg will occur only if 100 mg is well tolerated after reviewing the safety data up to 8 days post-dose as judged by the investigator. Sentinel dosing may be implemented in the 400 mg cohort as judged by the investigator: eg, 2 participants may be dosed prior to the remaining participants in Cohort 2. If the dose level is determined to have an acceptable safety and tolerability profile up to 8 days post-dose, as judged by the investigator for the first 2 sentinel participants, the remaining 7 participants in that cohort will be dosed. The total duration of each participation in this study is approximately 22 weeks, including a screening period of up to 4 weeks to confirm eligibility and a follow-up period of approximately 18 weeks after the single SC dose.

## 3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

As listed in Section 2.2 the primary and the other endpoints are related to ponsegromab serum PK and are described herein.

Samples for the PK analysis of ponsegromab will be taken according to the schedule of activities (SoA) given in the protocol.

Ponsegromab serum PK parameters (unbound and total) will be derived (if data permit) from the concentration-time profiles using standard non-compartmental methods as detailed in Table 2. Actual PK sampling times will be used in the derivation of ponsegromab serum PK parameters (unbound and total). In the case that actual PK sampling times are not available, nominal PK sampling times will be used.

**Table 2. Ponsegromab Serum PK Parameters (unbound and total)**

| Parameter | Definition | Method of Determination |
|---|---|---|
| $C_{max}$ | Maximum serum concentration | Observed directly from data |
| CCI [redacted] | [redacted] | [redacted] |
| $T_{max}$ | Time for $C_{max}$ | Observed directly from data as time of first occurrence |
| $t_{½}$[a] | Terminal half-life | $Log_e(2)/k_{el}$, where $k_{el}$ is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve |
| $AUC_{last}$ | Area under the serum concentration-time profile from time zero to the time of the last quantifiable concentration ($C_{last}$) | Linear/Log trapezoidal method |
| CCI [redacted] | [redacted] | [redacted] |
| $AUC_{inf}$[a] | Area under the serum concentration-time profile from time zero extrapolated to infinite time | $AUC_{last} + (C_{last}/k_{el})$, where $C_{last}$ is the predicted serum concentration at the last quantifiable time point estimated from the log-linear regression analysis |
| CCI [redacted] | [redacted] | [redacted] |

a. As data permit.

### 3.1. Primary Endpoint(s)

The primary endpoints are below ponsegromab serum PK parameters (unbound and total):

- $AUC_{inf}$, $AUC_{last}$, $C_{max}$, $T_{max}$, and $t_{½}$.

### 3.2. Secondary Endpoint(s)

The secondary endpoints include safety endpoints, which are described in Section 3.5.

CCI [redacted]

CCI [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

### 3.4. Baseline Variables

There are no baseline variables to be used as covariates or stratification factors in this study.

Baseline values are those collected on Day 1 prior to dosing, or the last pre-dose measurement collected on Day -1.

### 3.5. Safety Endpoints

#### 3.5.1. Adverse Events

An adverse event is considered a Treatment-Emergent Adverse Event (TEAE) if the event started during the effective duration of treatment. All events that start on or after the first dosing day and time/start time, if collected, but before the end of the study will be flagged as TEAEs. The algorithm will not consider any events that started prior to the first dose date.

#### 3.5.2. Laboratory Data

Safety laboratory tests will be performed as described in the protocol. Baseline is defined as the last pre-dose measurement collected on Day -1.

To determine if there are any clinically significant laboratory abnormalities, the hematology, chemistry, urinalysis and coagulation tests will be assessed against the criteria specified in Clinical Data Interchange Standards Consortium (CDISC) standard. The assessment will not take into account whether each participant's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

#### 3.5.3. Vital Signs Data

Supine blood pressure (BP) and pulse rate (PR) will be taken at times detailed in the SoA given in the protocol. When triplicate BP and PR are required, the average of the triplicate BP and PR measurements collected prior to dosing on Day 1 will serve as baseline. Change from baseline in supine BP and PR will be determined.

### 3.5.4. ECG Results

Supine triplicate 12-lead ECGs will be obtained at each assessment time indicated in the SoA given in the protocol. For each ECG parameter, the average of the triplicate readings collected at each assessment time will be used to represent a single observation. Baseline will be defined as the last pre-dose recordings on Day 1. Change from baseline in QT interval, heart rate, QTcF interval, PR interval, and QRS interval will be determined.

## 4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

For purposes of analysis, the following analysis sets are defined:

| Participant Analysis Set | Description | Applicable Analysis (for additional information refer to section 6) |
|---|---|---|
| Enrolled | "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. | |
| Safety Analysis Set | All enrolled participants who receive a dose of ponsegromab. Participants will be analyzed according to the product they actually received. | Secondary endpoints (section 6.2) |
| PK Concentration Analysis Set | All enrolled participants who receive a dose of ponsegromab and in whom at least 1 serum concentration value is reported. | Primary endpoints (section 6.1) |
| PK Parameter Analysis Set | All enrolled participants who receive a dose of ponsegromab and who have at least 1 of the serum PK parameters of interest calculated. | Primary endpoints (section 6.1) CCI [redacted] |
| [redacted] | [redacted] | [redacted] |

| Participant Analysis Set | Description | Applicable Analysis (for additional information refer to section 6) |
|---|---|---|
| CCI [redacted] | [redacted] | [redacted] |

## 5. GENERAL METHODOLOGY AND CONVENTIONS

### 5.1. Hypotheses and Decision Rules

There are no statistical hypotheses for this study.

### 5.2. General Methods

All data will be descriptively summarized.

Binary and categorical variables will be presented using summary statistics: number of observations and percentages.

Continuous variables will be presented using summary statistics: number of observations, arithmetic mean, standard deviation (SD), coefficient of variation (cv%), median, minimum, maximum, geometric mean and geometric cv%.

### 5.3. Methods to Manage Missing Data

#### 5.3.1. Safety Data

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied.

#### 5.3.2. Pharmacokinetic CCI [redacted] Data

**Concentrations Below the Limit of Quantification**

In all PK data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero.

In all CCI data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to the LLQ.

In listings, BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification (LLQ).

**Deviations, Missing Concentrations and Anomalous Values**

For PK [redacted] summary tables, plots of mean profiles and plots of median profiles, summary statistics will be calculated setting concentrations to missing if one of the following cases is true:

1. A concentration has been collected as ND (i.e., not done) or NS (i.e., no sample);

2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

**Pharmacokinetic [redacted] Parameters**

Actual PK[redacted] sampling times will be used in the derivation of PK[redacted] parameters.

If a PK[redacted] parameter cannot be derived from a participant's concentration data, the parameter will be coded as NC (i.e., not calculated). (Note that NC values will not be generated beyond the day that a participant discontinues.)

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular dose with ≥3 evaluable measurements.

If an individual participant has a known biased estimate of a PK[redacted] parameter (e.g., due to an unexpected event such as vomiting before all the compound is adequately absorbed in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics. For PK parameter calculations, the sponsor standard rules will be applied.

## 6. ANALYSES AND SUMMARIES

### 6.1. Primary Endpoint(s)

The ponsegromab serum PK parameters (unbound and total) detailed in Section 3.1 will be listed and descriptively summarized by cohort based on the PK parameter analysis set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.2. Each summary will include the set of summary statistics as specified in Table 3.

**Table 3. PK Parameters to be Summarized Descriptively**

| Parameter | Summary Statistics |
|---|---|
| $C_{max}$, [redacted] $AUC_{last}$, [redacted] $AUC_{inf}$, [redacted] | N, arithmetic mean, median, cv%, SD, minimum, maximum, geometric mean and geometric cv%. |
| $T_{max}$ | N, median, minimum, maximum. |

**Table 3. PK Parameters to be Summarized Descriptively**

| Parameter | Summary Statistics |
|---|---|
| $t_{½}$ | N, arithmetic mean, median, SD, minimum, maximum. |

CCI [redacted] Supporting data from the estimation of $t_{½}$ will be listed where applicable.

The serum ponsegromab concentrations (total and unbound) will be presented within the PK concentration analysis set (as defined in Section 4) and will include:

- a listing of all concentrations sorted by cohort, participant ID, study day, and nominal time post-dose. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.
- a summary of concentrations by cohort, study day, and nominal time post-dose, where the set of statistics will include number of observations, mean, median, SD, cv%, minimum, maximum and the number of concentrations above the LLQ.
- median concentration-time plots (on both linear and semi-log scales) against nominal time post-dose by cohort (all cohorts on the same plot per scale, based on the summary of concentrations by cohort and time post-dose).
- mean concentration-time plots (on both linear and semi-log scales) against nominal time post-dose by cohort (all cohorts on the same plot per scale, based on the summary of concentrations by cohort and time post-dose).individual concentration-time plots by cohort (on both linear and semi-log scales) against actual time post-dose.
- individual concentration-time plots (on both linear and semi-log scales) against actual time post-dose by cohort.

The scale used for the x-axis (time) of these plots will be decided on review of the data, and will depend on how long ponsegromab concentrations are quantifiable.

For summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used, for individual plots by time, the actual PK sampling time will be used. For pre-dose, the actual PK sampling time will be set to 0 hour.

### 6.2. Secondary Endpoint(s)

The details of safety analyses are described in Section 6.6.

CCI

[redacted]

CCI

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

### 6.4. Subset Analyses

No subset analyses will be performed.

### 6.5. Baseline and Other Summaries and Analyses

#### 6.5.1. Baseline Summaries

Demographic and baseline characteristics collected prior to the first dosing will be summarized following CDISC standard.

### 6.5.2. Study Conduct and Participant Disposition

Participant evaluation groups will show participant disposition. Frequency counts and percentages will be supplied for participant discontinuation(s). Data will be reported in accordance with CDISC standard.

### 6.5.3. Concomitant Medications and Nondrug Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be reported according to CDISC standard.

## 6.6. Safety Summaries and Analyses

Standard summary tables and listings will be generated in accordance with CDISC standard within safety analysis set (as defined in Section 4).

### 6.6.1. Adverse Events

All adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be listed and summarized by cohort.

### 6.6.2. Laboratory Data

Laboratory data will be listed and summarized by cohort. Baseline is as defined in Section 3.5.2.

Incidence of laboratory test (including hematological, clinical chemistry, coagulation test) abnormalities (without regard to baseline abnormality, with normal baseline and abnormal baseline, respectively) will be reported by cohort.

### 6.6.3. Vital Signs

Absolute values and changes from baseline in supine BP and PR will be summarized by cohort and study day. Tables will be paged by parameter. Baseline is as defined in Section 3.5.3.

Minimum and/or maximum absolute values and changes from baseline for supine BP and PR will also be summarized by cohort using categories as defined in Appendix 1. Numbers and percentages of participants meeting the categorical criteria will be provided. All planned and unplanned post-dose time points will be counted in these categorical summaries.

### 6.6.4. Electrocardiograms

Absolute values and changes from baseline in QT interval, heart rate, QTcF interval, PR interval, and QRS complex will be summarized descriptively by cohort and time. Tables will be paged by parameter. Baseline is as defined in Section 3.5.4.

Maximum and/or minimum absolute values and changes from baseline for ECG endpoints (QTcF interval, PR interval and QRS complex) will also be summarized by cohort using

categories as defined in Appendix 1. Numbers and percentages of participants meeting the categorical criteria will be provided. All planned and unplanned post-dose time points will be counted in these categorical summaries.

Listings of participants with any single post-dose value >500 msec will also be produced for QTcF.

## 7. INTERIM ANALYSES

### 7.1. Introduction

Interim analysis may be conducted for regulatory communication. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating PK[CCI] modeling, and/or supporting regulatory communication and clinical development.

### 7.2. Interim Analyses and Summaries

If an interim analysis is to be proceeded, analyses and summaries planned in this SAP may be conducted to support regulatory communication.

## 8. REFERENCES

None.

# 9. APPENDICES

## Appendix 1. Categorical Classes for ECG and Vital Signs Endpoints

### Categories for ECG Endpoints

| | | | |
|---|---|---|---|
| QTcF (msec) | 450< max. ≤480 | 480< max. ≤500 | max. >500 |
| QTcF (msec) increase from baseline | 30< max. ≤60 | max. >60 | |
| PR (ms) | max. ≥300 | | |
| PR (ms) increase from baseline | baseline >200 and max. ≥25% increase | baseline ≤200 and max. ≥50% increase | |
| QRS (ms) | max. ≥140 | | |
| QRS (ms) increase from baseline | ≥50% increase | | |

### Categories for Vital Signs Endpoints

| | | |
|---|---|---|
| Systolic BP (mm Hg) | min. <90 | |
| Systolic BP (mm Hg) change from baseline | max. decrease ≥30 | max. increase ≥30 |
| Diastolic BP (mm Hg) | min. <50 | |
| Diastolic BP (mm Hg) change from baseline | max. decrease ≥20 | max. increase ≥20 |
| Pulse rate (bpm) | min. <40 | max. >120 |

## Appendix 2. List of Abbreviations

| Abbreviation | Term |
|---|---|
| CCI | [redacted] |
| AE | adverse event |
| AUC | area under the curve |
| $AUC_{inf}$ | area under the concentration-time curve from time 0 to infinity |
| $AUC_{last}$ | Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration |
| BLQ | below the limit of quantitation |
| BP | blood pressure |
| bpm | beats per minute |
| CDISC | Clinical Data Interchange Standards Consortium |
| CCI | [redacted] |
| $C_{max}$ | maximum observed concentration |
| CRU | clinical research unit |
| CV | coefficient of variation |
| CCI | [redacted] |
| ECG | electrocardiogram |
| $k_{el}$ | first-order elimination rate constant |
| LLQ | lower limit of quantitation |
| MedDRA | Medical Dictionary for Regulatory Activities |
| msec | millisecond |
| CCI | [redacted] |
| NC | not calculated |
| ND | not done |
| NS | no sample |
| N/A | not applicable |
| CCI | [redacted] |
| PK | pharmacokinetic(s) |
| PR | pulse rate |
| QTcF | corrected QT |
| SAP | statistical analysis plan |
| SC | subcutaneous |
| SD | standard deviation |
| SoA | schedule of activities |
| $t_{1/2}$ | terminal elimination half life |
| TEAE | treatment-emergent adverse event |
| $T_{max}$ | time for $C_{max}$ |
| CCI | [redacted] |