Protocol C5301009

A PHASE 1, OPEN-LABEL, SINGLE DOSE STUDY TO INVESTIGATE THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF ZAVEGEPANT INTRANASAL ADMINISTRATION IN HEALTHY CHINESE ADULT PARTICIPANTS

Statistical Analysis Plan (SAP)

Version: 1

Date: 17 Apr 2023

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 17 Apr 2023	Original 20 Feb 2023	N/A	N/A

2. INTRODUCTION

The purpose of the study is to evaluate the pharmacokinetics (PK), safety, and tolerability of zavegepant following intranasal (IN) administration of 10 mg single dose in healthy Chinese adult participants. Results from this study will be used to support zavegepant 10 mg IN China registration for the acute treatment of migraine.

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C5301009. 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 systemic exposure of zavegepant following IN administration of 10 mg single dose in healthy Chinese adult participants.	• Zavegepant plasma PK parameters: C_{max}, AUC_{last}, and AUC_{inf} as data permits
Secondary:	**Secondary:**
• To assess the safety and tolerability of zavegepant following IN administration of 10 mg single dose in healthy Chinese adult participants. • To characterize the plasma PK profile of zavegepant following IN administration of 10 mg single dose in healthy Chinese adult participants.	• AEs, clinical safety laboratory tests, vital signs (BP and PR), physical examinations, and 12-lead ECGs. • Additional zavegepant plasma PK parameters: T_{max}, $t_{½}$, CL/F and Vz/F, as data permits

2.3. Study Design

This is a Phase 1, open-label, single dose study to characterize the PK, safety and tolerability of zavegepant in healthy Chinese adults following a single intranasal dose of 10 mg. Approximately 12 eligible participants, ages of 18 to 55 years (inclusive), will be enrolled in the study.

Screening evaluation will occur within 28 days prior to the study intervention administration (Day 1). Participants will be admitted to the clinical research unit (CRU) the day before Day 1 and will be kept under safety monitoring for 2 days at the CRU. Participants will receive 10 mg single dose of IN zavegepant on Day 1. The PK of zavegepant will be characterized following Day 1 dosing. A telephone follow-up will be made 28-35 days after the single dose.

This study will be conducted in a single center in China.

In this study, if more than 2 participants prematurely discontinue for reasons unrelated to the safety of the investigational product, participants may be replaced, at the discretion of the PI and sponsor study team.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

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

Zavegepant plasma PK parameters will be derived from the concentration-time profile using noncompartmental methods as detailed in Table 2. Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

Table 2. Zavegepant Plasma PK Parameters

Parameter	Definition	Method of Determination
C_{max}	Maximum plasma concentration	Observed directly from data
AUC_{last}	Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{inf}[a]	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time	$AUC_{last} + (C_{last}/k_{el})$, where C_{last} is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis

Table 2. Zavegepant Plasma PK Parameters

T_{max}	Time for C_{max}	Observed directly from data
$t_{½}$[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
CL/F[a]	Apparent clearance	$Dose/AUC_{inf}$
V_z/F[a]	Apparent volume of distribution	$Dose/(AUC_{inf} \times k_{el})$

a. If data permit.

3.1. Primary Endpoint(s)

The primary endpoints are zavegepant plasma PK parameters:

- C_{max}, AUC_{last}, and AUC_{inf} as data permits.

3.2. Secondary Endpoint(s)

- AEs, clinical safety laboratory tests, vital signs (BP and PR), physical examinations, and 12-lead ECGs.

- Additional zavegepant plasma PK parameters: T_{max}, $t_{½}$, CL/F and V_z/F, as data permits

3.3. Other Endpoint(s)

There are no other endpoints in the study.

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 (AE) 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, and urinalysis 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. The 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 Data

Standard 12-lead electrocardiograms (ECG) will be obtained at each assessment time indicated in the SoA given in the protocol. 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, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity. 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.	
PK Concentration Analysis Set	All enrolled participants who receive 1 single IN dose of zavegepant and provide at least 1 evaluable plasma concentration.	Primary endpoints (section 6.1) and secondary endpoints (additional PK parameter, section 6.2)

Participant Analysis Set	Description	Applicable Analysis (for additional information refer to section 6)
PK Parameter Analysis Set	All enrolled participants who receive 1 single IN dose of zavegepant and provide at least 1 evaluable PK parameters of interest.	Primary endpoints (section 6.1) and secondary endpoints (additional PK parameter, section 6.2)
Safety Analysis Set	All enrolled participants who receive 1 single IN dose of zavegepant. Participants will be analyzed according to the product they actually received.	Secondary endpoints (safety endpoints, section 6.2)

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 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 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 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 Parameters

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

If a PK 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 not be presented if more than 50% of the data are NC.

If an individual participant has a known biased estimate of a PK 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 zavegepant plasma PK parameters detailed in Section 3.1 will be listed and descriptively summarized 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}, AUC_{last}, AUC_{inf}, CL/F, and V_z/F	N, arithmetic mean, median, cv%, SD, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum.
$t_{½}$	N, arithmetic mean, median, SD, minimum, maximum.

For C_{max}, AUC_{last}, and AUC_{inf}, box and whisker plots for individual participant parameters overlaid with geometric means will be plotted. Supporting data from the estimation of $t_{½}$ will be listed where applicable.

The plasma zavegepant concentrations will be presented within the PK concentration analysis set (as defined in Section 4) and will include:

- a listing of all concentrations sorted by 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 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.
- mean concentration-time plots (on both linear and semi-log scales) against nominal time post-dose.
- individual concentration-time plots (on both linear and semi-log scales) against actual time post-dose.

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 zavegepant 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 6.5.

The additional zavegepant plasma PK parameters detailed in Section 3.2 will be summarized and plotted the same as the primary endpoints described in Section 6.1.

6.3. Subset Analyses

No subset analyses will be performed.

6.4. Baseline and Other Summaries and Analyses

6.4.1. Baseline Summaries

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

6.4.2. Study Conduct and Participant Disposition

A participant disposition table will be provided. Participant disposition will be summarized and will include the number and percentage of participants randomized, treated, completing and discontinuing from the study, the number of participants in each analysis population and reasons for discontinuation of study. The percentages will use the number of randomized as the denominator.

6.4.3. Concomitant Medications and Nondrug Treatments

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

6.5. 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).

6.5.1. Adverse Events

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be listed and summarized.

6.5.2. Laboratory Data

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

Incidence of laboratory test (including hematological, clinical chemistry and urine test) abnormalities (without regard to baseline abnormality) will be reported.

6.5.3. Vital Signs

BP and PR will be summarized using Pfizer's implementation of CDISC standards. For each planned timepoint, absolute values and change from baseline values will be summarized with descriptive statistics. Baseline is as defined in Section 3.5.3.

Minimum and/or maximum absolute values and changes from baseline for vital signs will also be summarized descriptively using categories as defined below. Numbers and percentages of participants meeting the categorical criteria will be provided.

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

6.5.4. Electrocardiograms

Absolute values and changes from baseline in QT interval, heart rate, QTcF interval, PR interval, and QRS complex will be summarized descriptively by time. 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 using categories as defined in below table. Numbers and percentages of participants meeting the categorical criteria will be provided.

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		

6.5.5. Other Safety Data

Medical history and physical examination collected during the course of the study, will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE.

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analysis will be conducted for this study.

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCES

None.

APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
AUC_{inf}	area under the plasma concentration-time profile from time 0 extrapolated to infinite time
AUC_{last}	area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})
BLQ	below the limit of quantitation
BP	blood pressure
CDISC	Clinical Data Interchange Standards Consortium
CL/F	apparent clearance
C_{max}	maximum plasma concentration
CRU	clinical research unit
CV	coefficient of variation
ECG	electrocardiogram
ID	identification
IN	intranasal
LLQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
NC	not calculated
ND	not done
NS	no sample
PI	Primary Investigator
PK	pharmacokinetic(s)
PR	Pulse rate
QTcF	corrected QT (Fridericia method)
SAP	statistical analysis plan
SD	standard deviation
SoA	schedule of activities
$t_{½}$	terminal half-life
TEAE	treatment emergent adverse event
T_{max}	time for C_{max}
V_z/F	apparent volume of distribution