Protocol *C3601007*

A PHASE I, SINGLE CENTER, OPEN LABEL STUDY TO ASSESS THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF AZTREONAM-AVIBACTAM ADMINISTERED AS SINGLE AND REPEATED INTRAVENOUS DOSES IN HEALTHY CHINESE SUBJECTS

Statistical Analysis Plan (SAP)

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Revision History			
Version	**Date**	**Author(s)**	**Summary of Changes/Comments**
Version 1.0	Sept 20, 2018	PPD	Initial Statistical Analysis Plan based on final Protocol of Aug 30, 2018

NOTE: Italicized text within this document has been taken verbatim from the Protocol.

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

None. This is the initial Statistical Analysis Plan, version 1.0.

2. INTRODUCTION

In order to facilitate development of ATM-AVI in China, this study will investigate the safety, tolerability and the PK after single and repeated IV infused doses of ATM with AVI to healthy male and female Chinese subjects. This study will be the first time to investigate PK profile of ATM when dosed in combination with AVI, evaluate the PK exposure of ATM when combined with AVI, and determine safety and tolerability of this combination in Chinese subjects.

2.1. Study Design

This is a Phase 1, single center, open label study to assess the PK, safety and tolerability of AVI in combination with ATM (ATM-AVI) administered as single and repeated IV infusion of doses in healthy Chinese subjects.

Twelve (12) healthy male and female Chinese subjects, aged 18 to 55 years, inclusive, will be recruited in this study in order to have at least 9 subjects complete the study procedures and have sufficient post-dose PK samples to calculate PK parameters.

The study will consist of a screening phase, a treatment phase and a follow-up phase. All screening evaluations will occur within up to 28 days prior to administration of the investigational product. All subjects will provide informed consent and undergo screening evaluations to determine their eligibility. Eligible subjects will check into the Clinical Research Unit (CRU) on Day -1. Subjects will receive a 3 hour IV infusion of 1500 mg ATM plus 500 mg AVI as a single dose on Day 1. Afterwards, subjects will receive a loading/extended loading dose followed by multiple doses of ATM-AVI IV infusion. The loading dose in this study is 500 mg ATM plus 167 mg AVI infused over a 30 minute period, immediately followed by an extended loading dose of 1500 mg ATM plus 500 mg AVI over a 3 hour period. Three (3) hours after the extended loading dose is completed, a maintenance dose of 1500 mg ATM and 500 mg AVI will be infused over 3 hours and administered q6h.

Serial blood samples and urine samples at specified intervals will be collected pre-dose and post-dose.

Detailed study activities are described in the SOA of the study protocol.

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2.2. Study Objectives

Primary Objective(s):

- *To investigate the PK of AVI administered in combination with ATM (ATM-AVI);*
- *To investigate the PK of ATM administered in combination with AVI.*

Secondary Objective(s):

- *To investigate the safety and tolerability of ATM-AVI as single and repeated intravenous (IV) infusions in healthy Chinese subjects.*

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No interim analysis is planned for this study. However, 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 dose-escalation decisions, facilitating PK/PD modeling, and/or supporting clinical development.

Final analysis will follow the official database release. As this will be an open-label study, there is no formal unblinding of the randomization code.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

No hypotheses are required.

4.2. Statistical Decision Rules

No decision rules are required.

5. ANALYSIS SETS

5.1. Pharmacokinetic (PK) Analysis Set

5.1.1. Concentration Analysis Set

The PK concentration population is defined as all subjects treated with study drug who have at least 1 ATM and AVI concentration measurement.

5.1.2. Parameter Analysis Set

The PK parameter analysis population is defined as all subjects treated with study drug who have at least 1 of the PK parameters of interest.

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5.2. Pharmacodynamic Analysis Set

None.

5.3. Safety Analysis Set

Safety analysis will be conducted in safety analysis set, ie, all subjects who received at least one dose of investigational product (ATM-AVI).

5.4. Other Analysis Sets

None.

5.5. Treatment Misallocations

All analyses will be performed on an "as-treated" basis and will not include data from subjects who are not treated.

If a subject takes a treatment that is not consistent with the treatment they are assigned to, for example takes a treatment out of sequence or takes the same treatment twice, then they will be reported under the treatment that they actually receive for all safety, PK and pharmacodynamic analyses, where applicable.

5.6. Protocol Deviations

Subjects who experience events that may affect their PK profile (eg lack of compliance with dosing) may be excluded from the PK analysis. At the discretion of the pharmacokineticist a concentration value may also be excluded if the deviation in sampling time is of sufficient concern or if the concentration is anomalous for any other reason.

A full list of protocol deviations will be compiled and reviewed to identify major and minor deviations prior to database closure.

5.6.1. Deviations Assessed Prior to Treatment Assignment

At Screening, the investigator will assess subjects against the inclusion and exclusion criteria as set out in Sections 4.1 and 4.2 of the protocol.

Deviations Assessed Post-Treatment Assignment

A full list of protocol deviations for the study report will be compiled prior to database closure. Any significant deviation from the protocol will be reviewed prior to database closure and a decision taken regarding evaluation for each analysis population.

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6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoint(s)

None.

6.2. Safety Endpoints

Any events occurring following start of treatment or increasing in severity will be counted as treatment emergent.

Events that occur in a non-treatment period (for example, Washout or Follow-up) will be counted as treatment emergent and attributed to the previous treatment taken.

The following data are considered in standard safety summaries (see protocol for collection days and list of parameters):

- *adverse events;*
- *laboratory data;*
- *vital signs data;*
- *ECG results.*

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6.3. Other Endpoints

6.3.1. PK Endpoints

Blood and urine samples for PK analysis of aztreonam and avibactam will be taken according to the Schedule of Activities in the protocol.

The following PK parameters will be calculated for aztreonam and avibactam (if possible) from the concentration-time data using standard noncompartmental methods (see the protocol Section 9.3 for detailed definition and method of determination):

Table 1. Noncompartmental PK Parameters

Matrix	PK Parameter	Analysis Scale	Aztreonam and Avibactam
Plasma	$AUC_{(0-6)}$, $AUC_{(0-24)}$, $AUC_{0-24,ss}$	ln	D
	AUC_{last}, $AUC_{0-\tau}$, AUC_{inf}	ln	D
	C_{max}, C_{min}	ln	D
	T_{max}	R	D
	$t_{1/2}^{*}$	R	D
	CL^{*}	ln	D
	V_{ss}, V_Z^{*}	ln	D
	RC_{max}, RAUC	R	D
Urine	CL_r	ln	D
	$Ae_{0-\tau}$	R	D
	$Ae_{0-\tau}$ (%)	R	D

Key: D=displayed with descriptive statistics, ln=natural-log transformed, R=raw (untransformed), *=if data permits, ss=steady state.

6.3.2. PD Endpoints

None.

6.4. Covariates

None.

7. HANDLING OF MISSING VALUES

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

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7.1. Concentrations Below the Limit of Quantification

In all 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.)

7.2. Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (ie, not done) or NS (ie, 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.

7.3. Pharmacokinetic Parameters

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

If a PK parameter cannot be derived from a subject's concentration data, the parameter will be coded as NC (ie, not calculated). (Note that NC values will not be generated beyond the day that a subject discontinues).

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

If an individual subject has a known biased estimate of a PK parameter (due for example 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 or statistical analyses.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

No formal statistical inference or statistical modeling will be performed. All PK parameters will be summarized descriptively.

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8.2. Statistical Analyses

The following PK parameters will be summarized descriptively:

Table 2. PK Parameters to be Summarized Descriptively by Treatment

Parameter	Summary Statistics
$AUC_{(0-6)}$, $AUC_{(0-24)}$, $AUC_{0-24,ss}$, AUC_{last}, $AUC_{0-\tau}$, AUC_{inf}, C_{max}, C_{min}, CL, CL_r, V_{ss}, V_Z	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum.
RC_{max}, RAUC, $t_{1/2}$, $Ae_{0-\tau}$, $Ae_{0-\tau}$%	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

Box and whisker plots for individual subject aztreonam and avibactam parameters ($AUC_{(0-6)}$, $AUC_{(0-24)}$, $AUC_{0-24,ss}$, $AUC_{0-\tau}$, AUC_{last}, AUC_{inf}, C_{max}, and C_{min}) will be presented overlaid with geometric means.

Supporting data from the estimation of t½ and AUC_{inf} will be listed by analyte: terminal phase rate constant (k_{el}); goodness of fit statistic from the log-linear regression (r^2); the percent of AUC_{inf} based on extrapolation ($AUC_{extrap\%}$); and the first, last, and number of time points used in the estimation of k_{el}. This data may be included in the appendix of clinical study report.

Concentrations will be listed and summarized descriptively by PK sampling time for Day 1 and Day 4. Summary profiles (means and medians) of the concentration-time data will be plotted for Day 1 and Day 4.

Presentations for aztreonam and avibactam concentrations will include:

- a listing of all concentrations sorted by subject ID, Day 1 and Day 4, and nominal time postdose. 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 Day 1 and Day 4, nominal time postdose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.

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- median concentrations time plots (on both linear and semi-log scales) by Day 1 and Day 4 against nominal time postdose.

- mean concentrations time plots (on both linear and semi-log scales) by Day 1 and Day 4 against nominal time postdose.

- individual concentration time plots (on both linear and semi-log scales) by Day 1 and Day 4 against actual time postdose (there will be separate spaghetti plots per scale).

For summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used, for individual subject plots by time, the actual PK sampling time will be used.

8.3. Safety Analysis

A set of summary tables will be produced to evaluate any potential risk associated with the safety and toleration of administering aztreonam and avibactam.

8.3.1. Treatment and Disposition of Subjects

Subject evaluation groups will show end of study subject disposition and will show which subjects were analyzed for pharmacokinetics, as well as for safety (adverse events and laboratory data). Frequency counts will be supplied for subject discontinuation(s) by treatment.

Data will be reported in accordance with the sponsor reporting standards.

8.3.2. Demographic and Clinical Examination Data

A break down of demographic data will be provided for age, race, weight, body mass index, and height. Each will be summarized by sex at birth and 'All Subjects' in accordance with the sponsor reporting standards.

8.3.3. Discontinuation(s)

Subject discontinuations, temporary discontinuations or dose reductions due to adverse events will be detailed and summarized.

Data will be reported in accordance with the sponsor reporting standards.

8.3.4. Adverse Events

Adverse events will be reported in accordance with the sponsor reporting standards.

8.3.5. Laboratory Data

Laboratory data will be listed and summarized in accordance with the sponsor reporting standards.

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8.3.6. Vital Signs Data

The baseline measurement is the predose measurement at hour 0 taken on Day 1.

For each planned timepoint, baseline values and change from baseline values will be summarized with descriptive statistics (using sponsor default standards).

These data will be listed in accordance with the sponsor reporting standards.

8.3.7. ECG Data

The baseline measurement is the predose measurement at hour 0 taken on Day 1.

For each planned timepoint, baseline values and change from baseline values will be summarized with descriptive statistics (using sponsor default standards).

These data will be listed in accordance with the sponsor reporting standards.

The average of the replicate readings collected for assessment times will be calculated prior to summarizing the data across subjects.

8.3.8. Other Safety Data

None.

8.3.9. Concomitant Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be provided in the listings.

8.3.10. Screening and Other Special Purpose Data

Prior medication(s) and non-drug treatment(s), serum FSH concentrations, urine drug screen, Pregnancy test, HIV, HepBsAg, HepBcAb, HCVAb testing, and History of tobacco, illegal drug and alcohol use will be obtained at Screening.

These data may not be brought in-house, and therefore may not be listed.

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9. REFERENCES

None.

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