Protocol C3591025

A PHASE 1, OPEN-LABEL, SINGLE-DOSE STUDY TO ASSESS THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF CEFTAZIDIME-AVIBACTAM (CAZ-AVI) IN CHILDREN FROM 3 MONTHS TO LESS THAN 18 YEARS OF AGE WHO ARE HOSPITALIZED AND RECEIVING SYSTEMIC ANTIBIOTIC THERAPY FOR SUSPECTED OR CONFIRMED NOSOCOMIAL PNEUMONIA, INCLUDING VENTILATOR-ASSOCIATED PNEUMONIA

Statistical Analysis Plan
(SAP)

Version: 2.0

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[redacted]

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1. VERSION HISTORY

Table 1. Summary of Changes

SAP Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
Version 1.0 27-Mar-2019	Original 17-Sep-2018	Not Applicable	This is the first version of this SAP
Version 2.0 02-Aug-2019	Amendment 1 12-Jun-2019	Changes were made for consistency with wording used in protocol amendment	Section 2 (Study Design): Updated texts in italics in several places from this section for consistency with the changes in protocol amendment • Section 2.2: clarification of the following: definition of nosocomial pneumonia, definition of evaluable subject for enrollment purposes, and late follow up visit. • Section 2.2.2: Updated schedule of assessments. Section 3 (Endpoints): Adjusted description of endpoints, which were also streamlined in protocol amendment • Section 3.1 Text for primary endpoints has been updated. • Section 3.1: Table 3 has been changed to reflect adjustments made in protocol to PK Blood Sample Assessments. • Section 3.3 Text for ELF by BAL endpoint has been updated. • Section 3.4 (Baseline variables): added text from protocol clarifying Screening (Day -1 to 1) and baseline assessments. Same change applies to Section 3.5.3. Section 6 (Analyses and Summaries): text was streamlined • Section 6.1 (Primary Endpoint – PK) and Section 6.3 (Other Endpoint – ELF by BAL): Provided further clarification regarding the summary of these endpoints. • Section 6.3 (Other Endpoint – ELF by BAL): added explanation on the derivation of CAZ and AVI ELF:plasma concentration ratios. • Section 6.5 (Baseline Summaries): provided definition of renal impairement. • Section 6.6.2. (Laboratory Data): clarified that laboratory results will be medically reviewed. • Sections 6.6.3 and 6.6.4 were added to describe summaries of study treatment exposure and prior/ concomitant medications, respectively.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study C3591025. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

Note: in this document any text taken directly from the protocol is *italicized*.

2.1. Study Objectives

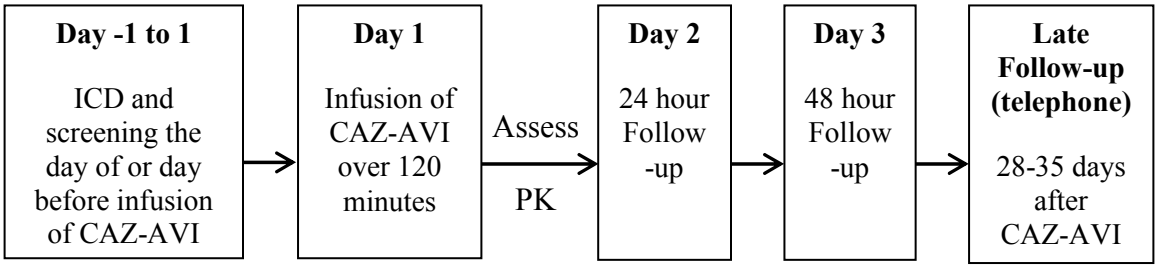
Primary Objective:
• *To characterize the pharmacokinetics (PK) of a single intravenous dose of CAZ-AVI in pediatric subjects aged 3 months to less than 18 years who are receiving systemic antibiotic therapy for suspected or confirmed nosocomial pneumonia, including ventilator-associated pneumonia.*
Secondary Objective:
• *To evaluate the safety and tolerability of a single intravenous dose of CAZ-AVI in pediatric subjects aged 3 months to less than 18 years with nosocomial pneumonia, including ventilator-associated pneumonia.*
Tertiary/Exploratory Objective:
• *To determine CAZ-AVI concentrations in bronchial epithelial lining fluid (ELF) by bronchoalveolar lavage (BAL) from subjects undergoing bronchoscopy for their clinical management if bronchoscopy with BAL is performed within the PK sampling interval after CAZ-AVI infusion.*

2.2. Study Design

This open label, single dose, PK *study aims to characterize the PK of CAZ-AVI and assess its safety and tolerability following a single IV infusion. Subjects will be hospitalized pediatric patients who are receiving systemic antibiotic therapy for suspected or confirmed nosocomial pneumonia (NP), defined as pneumonia with onset ≥48 hours after admission or within 7 days of discharge from an inpatient care facility, including ventilator-associated pneumonia (VAP), defined as a parenchymal lung infection arising ≥48 hours after endotracheal intubation and mechanical ventilation. Subjects will be enrolled in 4 cohorts of descending age, each consisting of at least 8 evaluable subjects. An evaluable subject is one who has received the complete single IV dose of CAZ AVI and provided PK blood samples at ≥50% of the sampling time points. The definition of an evaluable subject is used for enrollment purposes only, and does not impact the definition of the PK analysis set in* Section 4.4. *Each subject will receive a single IV dose of CAZ-AVI administered as an intravenous infusion over a 120 minute period. Blood samples will be collected from all subjects after the infusion to evaluate the PK of ceftazidime and avibactam. Subjects will be followed for 48 hours after the end of the infusion.*

The study will consist of a Screening visit (Visit 1, Day -1 to 1), during which consent will be obtained and subject eligibility will be confirmed, a Baseline/Treatment visit (Visit 2, Day 1) during which subjects will receive a single IV infusion of CAZ-AVI, and then two follow-up assessment visits at 24 hours (Visit 3, Day 2) and 48 hours (Visit 4, Day 3). A Late Follow-up (LFU) telephone visit will be conducted 28-35 days after the CAZ-AVI infusion to identify, assess, and record any new Serious Adverse Event (SAE). Blood samples for PK analyses (0.5 mL per sample) will be obtained over 22 hours following the CAZ-AVI infusion for Cohort 1 (7 samples), over 13 hours for Cohort 2 (6 samples), and over 6 hours for Cohorts 3 and 4 (4 samples). A Late Follow up (LFU) visit, that may be performed by telephone, will be conducted 28-35 days after the CAZ AVI infusion in order to identify, assess, and record any new Serious Adverse Event (SAE). The study outline is shown in Figure 1.

Figure 1. Study Outline



Subjects will be divided into 4 age cohorts, all enrolling simultaneously:

Cohort	***Age***	***Number***
1	*Age 12 years to <18 years*	*n=8*
2	*Age 6 years to <12 years*	*n=8*
3	*Age 2 years to <6 years*	*n=8*
4	*Age 3 months to <2 years (born ≥37 weeks gestational age)*	*n=8*
4a	*Age 1 year to <2 years*	*n=4*
4b	*Age 3 months to <1 year*	*n=4*

2.2.1. Sample Size Determination

This study is not powered for inferential statistical analysis. The sample size of 32 subjects is considered adequate to evaluate the pharmacokinetics of CAZ-AVI in this population.

2.2.2. Schedule of Activities

Table 2. Overview of the Protocol Visits and Procedures

Protocol Activity	*Screening*[a]	*Baseline/IV Infusion*	*24 hr Assessment*	*48 hr Assessment*	*Late Follow- up (LFU)*
Visit Number	*Visit 1*	*Visit 2*	*Visit 3*	*Visit 4*	*Visit 5*
Study Day	*Day -1 to 1*	*Day 1*	*Day 2*	*Day 3*	*Day 28-35*
Clinic Assessments					
Informed consent	X				
Demography	X				
Medical/surgical history	X				
Physical examination	X			X	
Inclusion/exclusion criteria	X				
Height	X[b]				
Weight	X[b]	X[a]		X	
Vital signs evaluation[c]	X	X	X	X	
Oxygen saturation (if available)	X	X	X	X	
Adverse Event and Serious Adverse Event assessment	X	X	X	X	X
Adjunctive therapeutic procedures (if any)		X	X	X	
Contraception check	X	X	X	X	X
CXR, CT scan, or other imaging tests	X[d]		X[e]		
Laboratory					
Hematology	X			X	
Blood chemistry	X	X[f]		X	
Urinalysis	X			X	
CrCL estimation[g]	X			X	
Pregnancy test[h]	X			X	
Study medication					
CAZ-AVI Infusion		X			
Pharmacokinetic (PK) blood sampling[i]		X			
BAL fluid collection for CAZ-AVI PK[j]		X			
Prior/Concomitant treatment[k]	X	X	X	X	

Abbreviations: CT scan = computed tomography scan; CXR = chest x-ray; IV = intravenous.

[redacted]

a. *Screening (Day -1 to 1) assessments will serve as baseline and can be completed on the same calendar day as Day 1, prior to CAZ-AVI infusion, but must be completed no earlier than the day before the start of CAZ-AVI infusion. If Screening and Baseline assessments are performed on different days, weight should be collected at both Screening and Baseline, and weight at Baseline should be used to calculate dose.*
b. *BMI will only be calculated at screening. The BMI will not be calculated for children <2 years of age as BMI is not considered a screening tool for healthy weight in children under 2 years of age.*
c. *Vital signs (blood pressure, pulse rate, respiratory rate and temperature) will be taken at the following time points: before infusion and at 2, 4, 6, 12, 24, and 48 hours after the end of CAZ-AVI infusion. Additional vital signs may be taken as needed.*
d. *At screening, obtain results of CXR, CT scan, or other imaging tests (eg, MRI, ultrasound) if performed as diagnostically part of the subject's regular medical care for the current diagnosis of pneumonia.*
e. *If clinically indicated.*
f. *Blood sample (0.5 mL) for blood urea analysis to be collected at the time of BAL only for subjects undergoing BAL as part of their clinical management.*
g. *Creatinine values will be used to calculate CrCL using the Bedside Schwartz equation [eGFR (ml/min/1.73 m^2) = 0.413 * (length(cm)/serum creatinine (mg/dL)], Schwartz, Munoz, et al., 2009.*
h. *A serum or urine pregnancy test with sensitivity for human chorionic gonadotropin (hCG) of at least 25 mIU/mL to be performed on all female subjects of childbearing potential (postmenarcheal), as determined by the Investigator.*
i. *PK samples will be drawn at time points indicated in Tables 3, 4 and 4 of the protocol for Cohort 1, Cohort 2, and Cohorts 3 and 4, respectively.*
j. *BAL fluid collection to be performed at selected sites only for subjects undergoing bronchoscopy with BAL as part of their clinical management during the time window for collection of PK blood samples after CAZ-AVI infusion. A matching blood sample to replace one of the PK blood samples is to be collected at the same time as the BAL, along with a blood sample for blood urea analysis.*
k. *Review prior and concomitant treatments. For Cohort 3 and 4 subjects who are being breast fed, record all medications taken by the lactating mother for 3 days before the CAZ-AVI infusion through Day 3.*

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints - PK

- *CAZ and AVI plasma concentrations by nominal time.*
- *CAZ and AVI PK parameters calculated by non-compartmental analysis (NCA) (Cohorts 1 and 2 only).*

Table 3. Schedule for PK Assessments. Nominal Times for Each Cohort

	Cohort 1	Cohort 2	Cohorts 3 and 4
	End of CAZ-AVI infusion/flush + 0 to 5 min (TPD 2h)	End of CAZ-AVI infusion/flush + 0 to 5 min (TPD 2h)	End of CAZ-AVI infusion/flush + 0 to 5 min (TPD 2h)
	30 min after the end of infusion/flush ± 5 min (TPD 2h 30)	15-45 min after the end of infusion/flush (TPD 2h 15)	15-45 min after the end of infusion/flush (TPD 2h 15)
	1.5h after the end of infusion/flush ± 15 min (TPD 3h 30)	1-2h after the end of infusion/flush (TPD 3h)	2-3h after the end of infusion/flush (TPD 4h)
	3h after the end of infusion/flush ± 30min (TPD 5h)	2-3h after the end of infusion/flush (TPD 4h)	4-6h after the end of infusion/flush (TPD 4h)
	6h after the end of infusion/flush ± 30 min (TPD 8h)	4-6h after the end of infusion/flush (TPD 6h)	
	10h after the end of infusion/flush ± 30 min (TPD 12h)	11-13h after the end of infusion/flush (TPD 13h)	
	22h after the end of infusion/slush ± 30 min (TPD 24h)		

The nominal time post-dose (TPD) as collected in the CRF is indicated in parenthesis

3.2. Secondary Endpoints - Safety

- *Safety and tolerability endpoints include adverse events (AEs), serious adverse events (SAEs), deaths, discontinuations due to AEs and laboratory abnormalities.*

3.3. Other Endpoints – ELF by BAL

CAZ and AVI ELF:plasma concentration ratios.

3.4. Baseline Variables

Baseline will be defined as the latest measurement taken prior to start of IV study drug. *Screening (Day -1 to 1) assessments will serve as baseline and can be completed on the same calendar day as Day 1, prior to CAZ AVI infusion, but must be completed no earlier than the day before the start of CAZ AVI infusion.*

3.5. Safety Endpoints

Clinical Data Interchange Standards Consortium (CDISC) and Pfizer Standards (CaPs) will be used for the analysis of standard safety data.

3.5.1. Adverse Events

An adverse event is considered treatment emergent relative to treatment if:

- the event occurs for the first time on or after the start of study treatment and was not seen prior to the start of treatment, or
- the event was observed prior to the start of study treatment but increased in severity during treatment.

The start of study treatment is defined as the start time of the infusion of IV study drug. Any adverse event that meets the requirements described above will be considered treatment emergent.

3.5.2. Laboratory Data

Laboratory data include hematology, blood chemistry, urinalysis and CrCL estimation, and will be collected at screening and at visit 4 (day 3, 48h assessment). Additional collection may be performed at Visit 2 (day 1) for those with BAL: Blood sample (0.5 mL) for blood urea analysis to be collected at the time of BAL only for subjects undergoing BAL as part of their clinical management.

3.5.3. Vital Signs, Height and Weight

Vital signs include blood pressure, pulse rate, respiratory rate and temperature and will be taken at the following time points: before infusion and at 2, 4, 6, 12, 24, and 48 hours after the end of CAZ-AVI infusion. Height will be collected at screening and weight will be collected at screening, baseline and at the 48h assessment. *If Screening and Baseline assessments are performed on different days, weight should be collected at both Screening and Baseline, and weight at Baseline should be used to calculate dose* and for summarization purposes.

4. ANALYSIS SETS

Data for all subjects will be assessed to determine if subjects meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per standard operating procedures.

4.1. Full Analysis Set

Not applicable, as there is no assessment of efficacy in this single dose study.

4.2. Per Protocol Analysis Set

Not applicable.

4.3. Safety Analysis Set

The safety analysis set will consist of all subjects who received any amount of IV study dose of CAZ AVI.

4.4. Pharmacokinetics Analysis Set

The PK analysis set will consist of all subjects who received a complete IV study dose of CAZ AVI and have at least 1 ceftazidime and/or avibactam plasma measurement available. All PK summaries will be presented using the PK analysis set.

5. GENERAL METHODOLOGY AND CONVENTIONS

The final analysis will be performed after dataset release.

5.1. Hypotheses and Decision Rules

The primary objective of this study is to evaluate the pharmacokinetics, safety, and tolerability of a single dose of CAZ-AVI in children with HAP/VAP. The study is not powered for inferential statistical analysis.

5.2. General Methods

Descriptive methods will be used to summarize all data. In general summaries will be presented overall and by cohort.

Descriptive methods for binary data will include counts and percentages.

In general, descriptive statistics for continuous data will include mean, standard deviation, median, minimum and maximum observed values. Continuous NCA PK parameters will also be summarized using geometric mean, and coefficient of variation.

5.3. Methods to Manage Missing Data

In general, missing values will not be imputed. Partial date handling will be done according to CaPs. Imputation of incomplete date of birth for the purposes of deriving age will follow the algorithm in Appendix 1.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s) – PK

Plasma concentrations of CAZ and AVI will be listed, and summarized by nominal time using appropriate descriptive statistics such as number, mean, SD, minimum, median, maximum, geometric mean, and coefficient of variation.

Individual plasma concentration profiles, using the PK analysis set for Cohorts 1 to 4, will be presented graphically using actual sample collection time on both linear and semilogarithmic scales, showing all patients on a single plot for each cohort and analyte. Median concentration time profiles will be presented on both linear and semilogarithmic scales using nominal time for both ceftazidime and avibactam.

In addition, PK parameters of ceftazidime and avibactam will be calculated by NCA using actual PK sampling times following single dose administration of CAZ-AVI for Cohorts 1 and 2 as described in Table 4.

For Cohorts 1 and 2 the NCA PK parameters will be summarized using descriptive statistics.

Further, the avibactam and ceftazidime concentration, pediatric patient demographics, and disease status data from Cohorts 1 to 4 will be combined with the data from appropriate previous clinical studies in pediatric patients and/or adults for a population PK analysis. The actual dosing and plasma sampling times will be used for the analysis. Individual compartmental PK parameters for pediatric patients in Cohorts 1 and 2 with available avibactam and ceftazidime plasma concentration data will be calculated by the empirical Bayesian estimate, and individual non-compartmental PK parameters such as C_{max}, minimum concentration (C_{min}), area under the plasma concentration time curves at steady state (AUC_{ss}), and $t_{½}$, will be derived from the determined avibactam and ceftazidime concentration time courses.

A stand alone population PK modelling and simulation analysis plan will be prepared and the results will be reported in a stand alone report outside of the clinical study report.

Table 4. PK parameters – non-compartmental analysis

Parameter	***Definition***	***Method of Determination***
AUC_{0-8}	*Area under the plasma concentration-time profile from time 0 to 8 hours*	*Linear/Log trapezoidal rule*
AUC_{inf}[a]	*Area under the plasma concentration-time profile from time 0 to infinity*	*Linear/Log trapezoidal rule* $AUC_{inf} = AUC_{last} + (C_{last}*/ k_{el})$, *where* $C_{last}*$ *is the estimated concentration at the time of the last quantifiable concentration and* k_{el} *is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression*
AUC_{last}	*Area under the plasma concentration-time profile from time 0 to the last quantifiable concentration*	*Linear/Log trapezoidal rule*
C_{max}	*Maximum plasma concentration*	*Observed directly from data*
T_{last}	*Time of last quantifiable plasma concentration*	*Observed directly from data*
T_{max}	*Time for* C_{max}	*Observed directly from data*
$t_{½}$[a]	*Terminal elimination half-life*	$Log_e(2)/k_{el}$
CL[a]	*Clearance*	$Dose/AUC_{inf}$
V_{ss}[a]	*Volume of distribution at steady-state*	*Volume of distribution at steady state is calculated as:* $V_{ss} = CL \times MRT$ *Mean residence time (MRT) is calculated as:* $MRT = AUMC_{inf}/AUC_{inf}$ *- (infusion time/2)* *Area under the first moment curve from 0 time to infinity (*$AUMC_{inf}$*) is calculated as:* $AUMC_{inf} = AUMC_{last} + ((t \times C_{est}^{1}*)/k_{el}) + (C_{est}^{1}*/k_{el}^{2})$ $^{1}C_{est} = e^{(-KEL \times Tlast)} \times KELC_0$ *, where* C_0 *is the back-extrapolated concentration at time zero*
V_z[a]	*Volume of distribution during terminal phase*	$Dose/(AUC_{inf} \times k_{el})$

a. If data permit.

6.2. Secondary Endpoints - Safety

The evaluation of safety and tolerability of a single IV dose of CAZ-AVI in this pediatric population is a secondary objective of this study. Safety endpoints are AEs, SAEs, deaths and discontinuations due to AEs, and laboratories abnormalities, therefore they will be summarized as per the CaPs standards. Further details are presented in Section 6.6.

6.3. Other Endpoint – ELF by BAL

CAZ and AVI ELF:plasma concentration ratios are defined as the ELF concentrations divided by the respective plasma concentration. This formula is only applicable for subjects who have BAL after bronchoscopy.

CAZ and AVI ELF:plasma concentration ratios are part of an exploratory objective for this study. Ceftazidime and avibactam ELF:plasma concentration ratios (for available matching ELF and plasma samples) will be listed. A listing of CAZ and AVI concentrations in BAL and urea concentrations in BAL and plasma will also be provided.

Parameter	Definition	Method of Determination
C_{BAL}	Drug Concentration in BAL*	Observed directly from data
$C_{urea,BAL}$	Urea concentration in BAL	Observed directly from data
$C_{urea,p}$	Urea concentration in blood plasma	Observed directly from data
C_{ELF}	concentration in ELF	$C_{BAL} \times (C_{urea,p}/C_{urea,BAL})$

* note that drug concentration is for both CAZ and AVI.

Example:

- C_{BAL}: CAZ concentration in BAL is 10 ng/mL
- $C_{urea,BAL}$: Urea concentration in BAL is 3 ng/mL
- $C_{urea,p}$: Urea concentration in plasma is 15 ng/mL
- C_{ELF}: CAZ concentration in ELF would be 50 ng/mL [calculated 10 x (15/3)]

CAZ and AVI ELF:plasma concentration ratios are part of an exploratory objective for this study. These ratios will be listed along with the CAZ and AVI concentrations in BAL and urea concentration in BAL and in blood plasma (for available matching ELF and plasma samples).

6.4. Subset Analyses

No subset analyses will be done for this study.

6.5. Baseline and Other Summaries and Analyses

CaPs standards will be used for the analysis of standard safety data:

- demographics;
- baseline characteristics (physical measurements, primary diagnosis, renal impairement: CrCL >= 50 and CrCL >=30 to <50 mL/min/1.73 m^2);
- medical and surgical history;
- physical examination;
- prior and concomitant treatments.

6.6. Safety Summaries and Analyses

No inferential statistical tests will be performed for any safety analyses.

6.6.1. Adverse Events

The incidence of AEs, SAEs, deaths, and discontinuations due to AEs will be summarized by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA), by relationship to study therapy, and by severity.

All recorded AEs will be listed and tabulated by system organ class, preferred term and for each cohort. Adverse events occurring from the start of study dose of CAZ-AVI infusion up to 48 hours after the end of infusion, and up to the end of the study (LFU) will be summarized by preferred term and system organ class using the MedDRA vocabulary (Version 14.0 or higher) by cohort.

6.6.2. Laboratory Data, Vital Signs, Physical Examination

For each safety parameter, the last assessment made before the first dose of study therapy will be used as the baseline for all analyses.

Descriptive statistics of observed results and the change from baseline to selected post baseline time points will be presented for clinical laboratory results and vital signs. Tabulations and listings of data for vital signs, physical examinations, and clinical laboratory tests will be presented with abnormal or out-of-range values flagged.

Potentially clinically significant laboratory results will be summarized. Laboratory data will be medically assessed for potential clinically significance, and summarized in the clinical study report through listings.

6.6.3. Study Treatment Exposure

Treatment exposure to CAZ-AVI will be summarized displaying counts and percentages of subjects who were exposed to each category of CAZ-AVI dose administered.

6.6.4. Prior and Concomitant Medications

Prior and concomitant medications received by the subject (and for the mothers of breast-fed subjects in cohorts 3 and 4) will be summarized using standard summaries.

7. INTERIM ANALYSES

7.1. Introduction

This is an open-label, single arm study. All the interim analyses described in this section are for descriptive purposes.

7.2. Interim Analyses and Summaries

No formal interim analysis will be conducted 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 pharmacokinetic (PK)/pharmacodynamic (PD) modeling, and/or to support clinical development.

7.3. Data Monitoring Committee

This study will not have an external data monitoring committee (E-DMC).

7.4. Safety Review Committee

This study will use an Internal Safety Review Committee which will be known as the Safety Review Committee (SRC). The SRC will consist of the study team physician, international coordinating Investigator or delegate, global safety/risk lead or delegate, therapeutic area director or delegate and the clinical pharmacologist/pharmacometrician or delegate. The SRC will assess safety and tolerability after the first 4 subjects in each cohort are enrolled. With the exception of the international coordinating Investigator or delegate, all members of the SRC will be members of the Sponsor organization. Other team members may be asked to join as needed.

8. APPENDICES

Appendix 1. Imputation of Incomplete Date of Birth and Derivation of Age - Cohort 4

For subjects in Cohort 4 date of birth will be collected as month and year (ie, day will be unknown). Imputation of incomplete date of birth (DOB) will be done using the following data available from the case report form: month and year of birth from the in complete DOB, date of informed consent, expected age in months for cohorts 4a and 4b.

- Step 1. Find a range of plausible DOBs based on the known month and year of birth from the incomplete DOB;
- Step 2. Find a range of plausible DOBs based on the date of informed consent and the expected age in months for each cohort according to Table 5;
- Step 3. Determine the range of possible DOBs based on the intersection of the two ranges in Steps 1 and 2[a];
- Step 4. Use the midpoint of the range of possible DOBs in Step 3 as the imputed DOB; derive age in months by subtracting the imputed DOB from the date of informed consent, and dividing by 30.42.

Note:

a. if the ranges of plausible DOBs found in Steps 1 and 2 are not overlapping and the data for incomplete DOB and date of informed consent are confirmed by the site to be correct, this represents a protocol deviation on the age of patients. In this case, the range of possible DOBs in Step 3 will be determined based on the range from Step 1 and the date of informed consent, without taking the expected age of the cohorts into consideration.

For example, a patient from Cohort 4a:

- incomplete DOB of Aug2017, date of informed consent 01Dec2018;
- Step 1 range: 01Aug2017 to 31Aug2017;
- Step 2 range: 02Dec2016 (i.e., almost 2 years old) to 01Dec2017 (ie, 1 year old);
- Step 3 range: 01 to 31Aug2017;
- Step 4: imputed DOB is 16Aug2017, derived age is 472 days, or 15.5 months.

Table 5. Expected Age Ranges for Cohorts 4a and 4b

Cohort	Age Range	Expected age in Months
4a	Age 1 year to <2 years	12 to <24
4b	Age 3 months to <1 year	3 to <12

Appendix 2. Imputation of Incomplete Date of Birth and Derivation of Age – Cohorts 1, 2 and 3

For subjects in Cohorts 1, 2 and 3 date of birth will be collected only as year (i.e., both day and month will be unkown). Imputation of incomplete date of birth (DOB) will be done using the following data available from the case report form: year of birth from the incomplete DOB, date of informed consent, expected age in years cohorts 1, 2 and 3.

- Step 1. Find a range of plausible DOBs based on the year of birth from the incomplete DOB;
- Step 2. Find a range of plausible DOBs based in the date of informed consent and the expected age in years for each cohort according to Table 6;
- Step 3. Determine the range of possible DOBs based on the intersection of the two ranges in Steps 1 and 2a;
- Step 4. Use the midpoint of the range of possible DOBs in Step 3 as the imputed DOB; derive age in years by subtracting the imputed DOB from the date of informed consent, and dividing by 365.25.

Note:

a. if the ranges of plausible DOBs found in Steps 1 and 2 are not overlapping and the data for incomplete DOB and date of informed conset are confirmed by the site to be correct, this represents a protocol deviation on the age of patients. In this case, the range of possible DOBs in Step 3 will be determined based on the range from Step 1 and the date of informed consent, without taking the expected age of the cohorts into consideration.

For example, a patient from Cohort 1:

- incomplete DOB UNK/UNK/2006, and informed consent date 01Jul2018;
- Step 1 range: 01Jan2006 to 31Dec2006;
- Step 2 range: 02Jul2000 (ie, is almost 18 years old) to 01Jul2006 (ie, 12 years old);
- Step 3 range: 01Jan2006 to 01Jul2006;
- Step 4: imputed DOB is 01Apr2006, derived age is 4474 days, ie, 12.2 years.

Table 6. Expected age ranges for cohorts 1, 2 and 3

Cohort	Age Range in years
1	Age 12 years to <18 years
2	Age 6 years to <12 years
3	Age 2 years to <6 years