Protocol C3591024

A PHASE 2A, 2-PART, OPEN-LABEL, NON-RANDOMIZED, MULTICENTER, SINGLE AND MULTIPLE DOSE TRIAL TO EVALUATE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF CEFTAZIDIME AND AVIBACTAM IN NEONATES AND INFANTS FROM BIRTH TO LESS THAN 3 MONTHS OF AGE WITH SUSPECTED OR CONFIRMED INFECTIONS DUE TO GRAM-NEGATIVE PATHOGENS REQUIRING INTRAVENOUS ANTIBIOTIC TREATMENT

Statistical Analysis Plan (SAP)

Version: 2.0

Date: 18-Sep-2019

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
Version 1 27-Dec-2018	Original 11-Jul-2018	N/A	N/A
Version 2 18-Sep-2019	Amendment 1 27-Jun-2019	Changes were made for consistency with wording used in protocol amendment 1	• Table 2 in Section 2.2 has been revised to clarify that the upper limit of age described in inclusion criterion for Cohort 1 as <3 months corresponds to <89 days. Text for the definition of corrected age in the footnote of this table was expanded, and reference was made to Appendix 2 of the protocol. These revisions also apply to Table 6 of Appendix 2. • Analysis of the description of PK endpoints in Sections 3.1 and 3.2 were simplified. • It has been clarified in Section 4.4 that subjects in Part B only must meet at least 1 clinical and 1 laboratory criterion or meet at least 2 of the clinical criteria to be included in the Modified ITT analysis set. • It has been clarified in Section 4.5 that in Part A the PK analysis set requires subjects to have the single dose of CAZ-AVI (and not any amount) and in Part B, it requires subjects to have at least 3 consecutive doses of CAZ AVI (and not 48 hours). • Text was updated in Sections 5.2 and 6.1 to use 'nominal sampling time' uniformly throughout the document in the description of the pharmacokinetic endpoint, for consistency with the description of PK endpoints in Section 2 of the protocol and in Section 3 of the SAP. • A paragraph was added to Section 6.2.3.1 to determine the use of central versus local lab results when determining baseline pathogens and their susceptibility. • In section 6.2.3.2. the definition of per-subject microbiological response in Table 4 has been revised to reflect the changes to Table 7 of the protocol. • It has been clarified in section 6.6.2 how potentially clinically significant laboratory results will be summarized. • Treatment exposure in Section 6.6.4 has been expanded to distinguish between the summaries

			for Part A (in hours) and Part B (in calendar days, in addition to number of infusion). • Section 7.4 of the SAP has been revised to reflect change to Part B Cohort 3 enrollment sequence in the protocol as requested by the EMA Pediatric Committee (PDCO) on 19 Oct 2018. Figure 3 was added to SAP to illustrate this change as per protocol amendment 1.
		Review from microbiologist	• Appendix 1. Added *Kluyvera Intermedia* and *Providencia Stuartii* to the list of pathogens.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study C3591024. 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

Part A Primary Objective:
To characterize the pharmacokinetics (PK) of a single intravenous dose of CAZ-AVI in hospitalized neonates and infants from birth to <3 months.
Part A Secondary Objective:
To evaluate the safety and tolerability of a single intravenous dose of CAZ-AVI in hospitalized neonates and infants from birth to <3 months.

Part B Primary Objective:
To evaluate the safety and tolerability of CAZ-AVI for the treatment of aerobic Gram-negative infection in neonates and infants from birth to <3 months.
Part B Secondary Objectives:
To evaluate the pharmacokinetic profile of multiple intravenous doses of CAZ-AVI in hospitalized neonates and infants from birth to <3 months.
To evaluate the efficacy of CAZ-AVI for the treatment of aerobic Gram-negative infection in neonates and infants from birth to <3 months.

2.2. Study Design

This is a 2-part Phase 2a non-randomized, multicenter, open-label, single and multi-dose PK study to assess PK, safety, and tolerability of CAZ-AVI in neonates and young infants aged birth to <3 months. The efficacy of CAZ-AVI for the treatment of aerobic Gram-negative infection will be summarized descriptively as a secondary objective in the multi-dose portion of the trial.

This study is not randomized. All enrolled subjects will receive CAZ-AVI either as a single dose in Part A or multiple doses in Part B. A total of 48 subjects are planned to be enrolled; 24 in Part A and 24 in Part B. *The study outline is provided in* Figure 1.

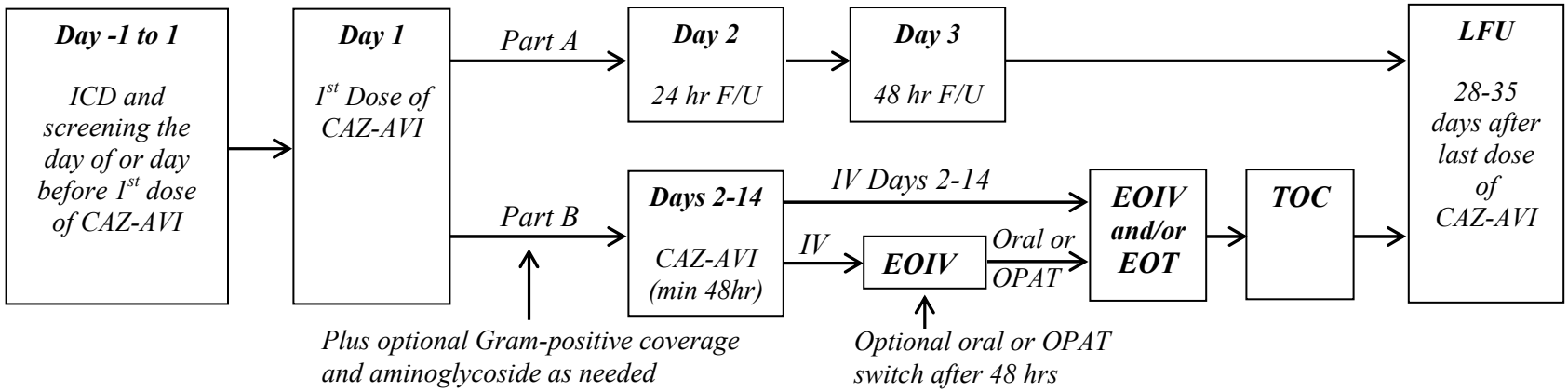
Parts A and B will each be divided into 3 age cohorts according to Table 2.

Table 2. Definition of Age Cohorts

Cohort	*Age*	*Part A*	*Part B*
1	*Term infants (GA ≥37 weeks) age >28 days to <3 months (<89 days) or pre-term infants with corrected age >28 days to <3 months (<89 days)*	*n=8*	*n=8*
2	*Term neonates (GA ≥37 weeks) from birth to ≤28 days*	*n=8*	*n=8*
3	*Pre-term neonates (GA ≥26 to <37 weeks) from birth to ≤28 days*	*n=8*	*n=8*

GA = Gestational Age , the time elapsed between the first day of the last menstrual period and birth; Corrected age is the age of the infant from the expected date of delivery, calculated by subtracting the number of weeks born before 40 weeks of gestation from the chronological age. Corrected age (weeks) = chronological age in weeks – (40 – gestational age in weeks). See Appendix 2 of protocol for calculation of corrected age in days and alternative perinatal age terminologies.

Figure 1. ***Study Outline***



Abbreviations: CAZ-AVI = ceftazidime-avibactam; EOIV = End of IV; EOT = End of Treatment; F/U = Follow-Up; hr(s) = hour(s); ICD = Informed Consent Document; IV = Intravenous; LFU = Late Follow-Up; OPAT = outpatient parenteral antimicrobial therapy; TOC = Test of Cure.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints (PK for Part A, Safety for Part B)

Part A: *CAZ and AVI plasma concentration by nominal sampling time*.

Part B: *safety and tolerability endpoints including adverse events (AEs), serious adverse events (SAEs), deaths, discontinuations due to AEs and laboratory abnormalities.*

3.2. Secondary Endpoints (Safety for Part A, PK and efficacy for Part B)

Part A: *safety and tolerability endpoints including adverse events (AEs), serious adverse events (SAEs), deaths, discontinuations due to AEs and laboratory abnormalities.*

Part B: *CAZ and AVI plasma concentration by nominal sampling time.*

Efficacy secondary outcome measures for Part B include:

- *All-cause mortality.*
- *Clinical outcome at EOIV, EOT, TOC and LFU.*
- *Cure defined as clinical improvement and no need for further antibacterial treatment, 7 to 14 days after end of treatment.*
- *Microbiological eradication 7 to 14 days after end of treatment.*
- *Emergent infections.*

3.3. Other Endpoints

Not applicable.

3.4. Baseline Variables

Baseline will be defined as the latest measurement taken prior to start of IV study drug, unless otherwise specified. The baseline assessment for vital signs that have multiple measures within one visit such as systolic and diastolic blood pressure, pulse and respiratory rates and oxygen saturation will be the average of the measurements within that visit. If multiple measures of temperature are available within one visit, the highest value will be summarized.

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 first infusion of IV study drug. No lag time will be defined, ie, any adverse event that meets the requirements described above will be considered treatment emergent.

3.5.2. Laboratory Data

Laboratory data include urine output, blood chemistry, hematology and urinalysis.

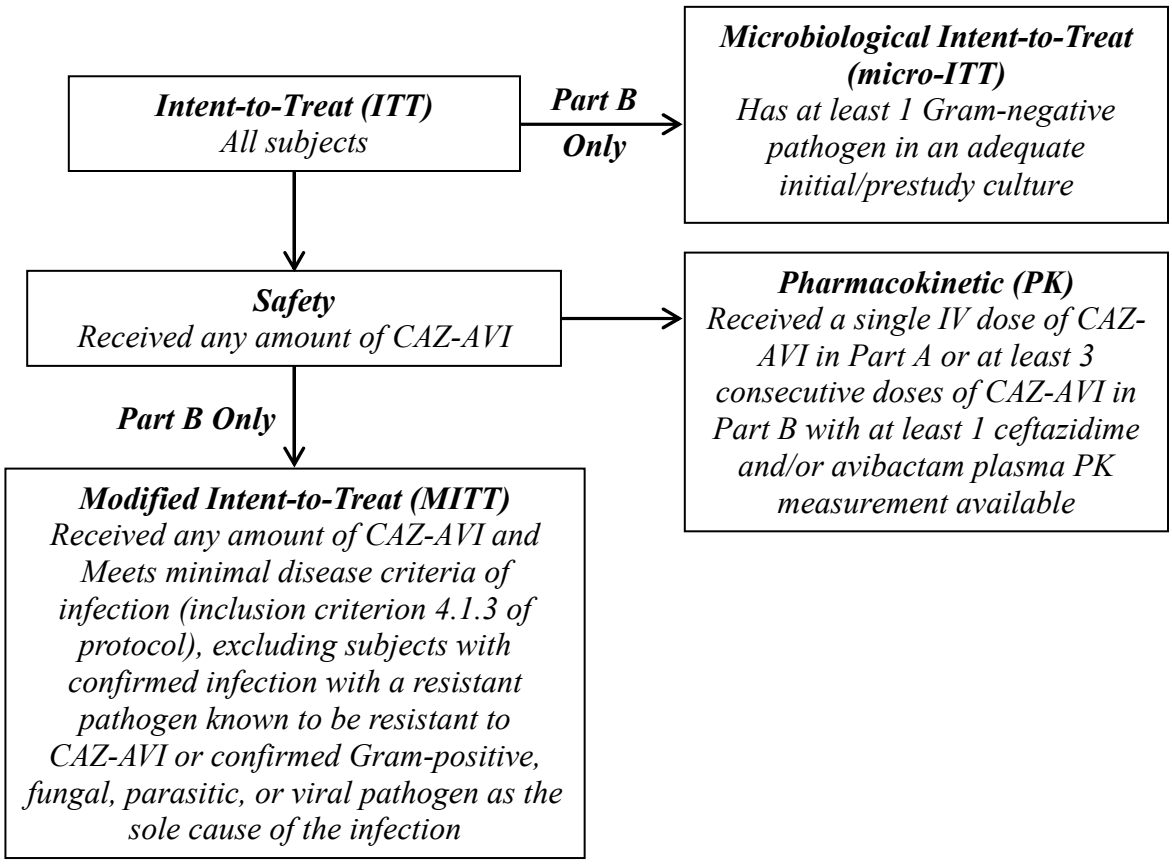
3.5.3. Vital Signs, Weight and Body Length

Vital signs measures include temperature (C), systolic and diastolic blood pressure (mmHg), pulse rate (beats/min) , respiratory rate (breaths/min) and oxygen saturation (%). Weight (kg) and body length (cm) will be summarized along with vital signs.

4. ANALYSIS SETS

Analysis sets are described in the sections below and in Figure 2.

Figure 2. ***Study Analysis Sets***



Abbreviations: CAZ-AVI = ceftazidime-avibactam; PK = pharmacokinetic.

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 (Parts A and B)

The full analysis sets for Part A and Part B are each defined as all subjects who have been enrolled in each part of the study, regardless of whether or not treatment was received. These analysis sets will be referred to in the summary outputs as intent-to-treat (ITT).

4.2. Per Protocol Analysis Set

There will not be a Per Protocol Analysis Set for this study.

4.3. Safety Analysis Set (Part A and Part B)

The Safety Analysis Sets for Part A and Part B are each defined as those subjects who received any amount of the investigational drug (CAZ-AVI) in the respective part. The safety analysis set is the primary population for treatment administration/compliance and safety.

4.4. Efficacy Analysis Sets (Part B only)

For Part B only, two efficacy analysis sets are defined:

> ***Modified Intent-to-Treat (MITT):*** *Received any amount of CAZ-AVI and meets minimal disease criteria of infection described in protocol inclusion criterion 4.1.3 (defined as the presence of at least 1 clinical criterion and 1 laboratory criterion or meet at least 2 clinical criteria in the presence of, or as a result of suspected or proven bacterial infection requiring IV antibiotic therapy). Subjects with confirmed infection with a pathogen known to be resistant to CAZ-AVI and subjects with a confirmed Gram-positive, fungal, parasitic, or viral pathogen as the sole cause of infection will be excluded.* A list of microorganisms that are considered pathogens is provided in Appendix 1.
>
> ***Microbiological Intent-to-Treat (micro ITT):*** *Has at least 1 Gram-negative pathogen in an adequate initial/prestudy culture.*

4.5. Pharmacokinetic Analysis Set (Part A and part B)

The Pharmacokinetic (PK) analysis set for Part A is defined as subjects who received a single IV dose of CAZ-AVI in Part A. The PK analysis set for Part B is defined as subjects who received at least 3 consecutive doses of CAZ-AVI in Part B. In order for a subject to be part of the PK analysis sets he/she must have at least 1 ceftazidime and/or avibactam plasma PK measurement available.

In case of partial IV dose of CAZ-AVI, patients may be included in the PK analysis set as long as they have at least one PK measurement and received a quantifiable dose of CAZ-AVI (based on the rate and the duration of the infusion).

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 CAZ-AVI in neonates and young infants with bacterial infections. Limited efficacy information will be available as a secondary objective of Part B. 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 separately for Part A and Part B, unless otherwise stated.

Descriptive methods for binary data will include counts and percentages, and 95% confidence interval for proportions when applicable.

In general, descriptive statistics for continuous data will include mean, standard deviation, median, minimum and maximum observed values. *For each Part, A and B and each Cohort 1, 2, and 3, the plasma concentration will be summarized by nominal sampling time using appropriate descriptive statistics (eg, number, mean, standard deviation (SD), minimum, median, maximum, 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 2.

6. ANALYSES AND SUMMARIES

6.1. Pharmacokinetic Analysis (Primary Objective Part A, Secondary Objective Part B)

The PK analysis set defined in Section 4.5 will be used for all PK analysis.

A listing of ceftazidime and avibactam plasma concentrations at the nominal sampling times by subject, cohort and Part will be provided. For each Part, A and B and each Cohort 1, 2, and 3, the plasma concentration will be summarized by nominal sampling time using appropriate descriptive statistics (eg, number, mean, standard deviation (SD), minimum, median, maximum, geometric mean, and coefficient of variation).

Individual plasma concentration profiles will be presented graphically using actual sample collection time on both linear and semilogarithmic scales, showing all subjects on a single plot for each cohort and analyte. Median concentration-time profiles will be presented on both linear and semilogarithmic scales using nominal sampling time for both ceftazidime and avibactam. Additional graphical presentations of PK data may be included at the discretion of the PK scientist.

In addition, the avibactam and ceftazidime concentration, pediatric subject demographics, and disease status data from Cohorts 1 to 3 will be combined with the data from appropriate previous clinical studies in pediatric subjects and/or adults for a population PK analysis. The actual dosing and plasma sampling times will be used for the analysis. A stand-alone population PK modelling and simulation analysis plan will be prepared and the results will be reported in a stand-alone report, for each Part A and Part B, outside of the clinical study report.

6.2. Efficacy Analysis (Secondary Objective Part B)

6.2.1. All-cause Mortality

All cause mortality will be summarized with counts and proportions of deaths and 95% confidence intervals when applicable, for the ITT analysis set.

6.2.2. Clinical Outcome

An assessment of clinical outcome will be made by the Investigator at EOIV, EOT, TOC and LFU. An outcome of clinical failure at EOIV will be carried forward to the subsequent visits.

Possible outcomes are clinical cure, clinical improvement (oral/OPAT switch subjects only)), clinical failure, or indeterminate. A favorable clinical outcome is clinical cure or clinical improvement.

Clinical outcomes will be summarized descriptively for all efficacy analysis sets from Part B: ITT, MITT, and micro-ITT. For each nominal timepoint (EOIV, EOT, TOC, and LFU) proportions of subjects with each clinical outcome, and with a favorable clinical outcome will be displayed overall and within each cohort.

Counts and proportions of patients with a clinical outcome of cure 7 to 14 days after end of treatment (ie, at TOC) will be presented along with a 95% confidence interval.

6.2.3. Microbiological Response

Summaries of microbiological responses will be presented only for the micro-ITT analysis set.

6.2.3.1. Per-pathogen Microbiological Response

The per-pathogen microbiological outcome categories at TOC are defined in Table 3. *Favorable microbiological outcomes are eradication or presumed eradication.*

Table 3. Per-Pathogen Microbiological Outcomes Categories at TOC

Microbiological Response[a]	***Definition***
Eradication	*Source specimen demonstrated absence of the original baseline pathogen*
Presumed eradication	*Source specimen was not available to culture and the subject was assessed as a clinical cure*
Persistence	*Source specimen demonstrates continued presence of the original baseline pathogen*
Presumed persistence	*Source specimen was not available to culture and the subject was assessed as a clinical failure*
Indeterminate	*Source specimen was not available to culture and the subject's clinical outcome was assessed as indeterminate*

Abbreviations: TOC=Test of Cure.

a. *For subjects who are clinical failures before TOC, the microbiological outcome will be carried forward to TOC and will be determined based on the cultures and/or clinical outcome at the time of the early clinical failure determination.*

Baseline pathogen data *will be determined based on central laboratory data. In the absence of any baseline central laboratory data, then local laboratory data will be used to identify baseline pathogens* and their susceptibility. A list of microorganisms that are considered to be pathogens are described in Appendix 1.

When available, results from the central laboratory for the multi-locus sequence typing (MLST) will be used to determine eradication or persistence on microorganisms of the same species isolated at baseline and post-baseline. Otherwise persistence/eradication will be determined based on the species.

Per-pathogen summaries: Counts and proportions of pathogens with each per pathogen microbiological response (eradication, presumed eradication, persistence, presumed persistence or indeterminate) at TOC will be summarized, and the proportion of pathogens with a favorable per-pathogen microbiological response (eradication or presumed eradication) will be presented along with a 95% confidence interval.

Per-pathogen listings: Where applicable, the β-lactmases of Gram negative pathogens based on the MIC profile from any baseline or post-baseline isolates will presented in a listing.

6.2.3.2. Per-subject Microbiological Response

Per-subject microbiological response at TOC will be determined programmatically based on individual outcomes for each baseline pathogen, as per Table 4.

Table 4. Per-subject Microbiological Response

Number of pathogens at baseline	***Pathogen 1 Outcome at TOC***	***Pathogen 2 Outocome at TOC***	***Per-Subject microbiological Response at TOC***
1 pathogen	*Favorable*		*Favorable*
	Unfavorable		*Unfavorable*
	Indeterminate		*Indeterminate*
2 pathogens	*Favorable*	*Favorable*	*Favorable*
		Unfavorable	*Unfavorable*
		Indeterminate	*Indeterminate*
	Unfavorable	*Any result*	*Unfavorable*
	Indeterminate	*Favorable*	*Indeterminate*
		Unfavorable	*Unfavorable*
		Indeterminate	*Indeterminate*

Per-subject summaries: Counts and proportions of subjects with each a favorable microbiological response at TOC will be presented along with a 95% confidence interval.

6.2.3.3. Emergent Infections

Pathogens first appearing after Baseline ("emergent infections") until the LFU are categorized as in Table 5*, using microbiological laboratory results. Counts and percentages of the number of subjects with a new infection and with a super infection will be presented.*

Table 5. Emergent Infections

Emergent Infections	***Definition***
Superinfection	*A culture identified pathogen other than a baseline pathogen during the course of active treatment with study therapy requiring alternative antimicrobial therapy.*
New infection	*A culture identified pathogen other than a baseline pathogen at any time after study treatment has finished requiring alternative antimicrobial therapy.*

6.3. Other Endpoint(s)

Not applicable.

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 (age, gestational age, gender, race and ethnicity);
- Baseline characteristics (primary diagnosis, breast feeding);
- Medical history;
- Physical exam;
- Signs and symptoms.

Baseline pathogens will summarized by presenting the number and percentage of subjects with each pathogen.

6.6. Safety Summaries and Analyses

6.6.1. Adverse Events

Parts A and B will be summarized separately in addition to an overall safety summary (ie, Part A and B patients in one single AE summary table). *No inferential statistical tests will be performed for any safety analyses. The incidence of treatment emergent AEs, SAEs, deaths, and discontinuations due to AEs will be summarized by system organ class and preferred term according to the current version at time of study reporting of 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.*

In addition to the above mentioned summaries of AEs, the incidence of treatment emergent AEs up to EOIV will also be summarized for patients in Part B.

6.6.2. Laboratory Data

Descriptive statistics of observed results and the change from baseline to selected postbaseline time points (Days 2 and 3 for Part A; EOIV, EOT, TOC, LFU for Part B) will be presented for clinical laboratory results. Shift tables will summarize the number of patients who have a shift in categories of laboratory data from baseline to worst value up to end of IV treatment (Part B only) and from baseline to worst value anytime in study up to LFU.

Listings of data for clinical laboratory tests will be presented with abnormal or out-of-range values flagged for each patient*. 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. Vital Signs, Weight and Body Length

Tabulations and listings of data for vital signs, weight, body length, and physical examinations tests will be presented.

6.6.4. Study Treatment Exposure

For Part A treatment exposure will be summarized with descriptive statistics (mean, SD, median, range) of the duration (in hours) of the single dose of CAZ-AVI

For Part B treatment exposure to CAZ-AVI will be summarized with descriptive statistics of the number of calendar days subjects were exposed to CAZ-AVI, with counts and percentages of subjects who were exposed to each category of number of days of exposure and also with descriptive statistics of the total number of IV infusions received by patients. Summaries will also be presented for the number of days subjects were exposed to oral/OPAT treatment for infection and also for the overall combined number of days subjects were exposed to CAZ-AVI and oral/OPAT treatment.

6.6.5. Prior and Concomitant Medications

Prior and concomitant medications received by the subject and by the mother of subjects who are being breastfed will be summarized using standard summaries. Separate summaries will be presented for antibiotic medications and medications other than systemic antibiotics.

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

An interim report summarizing the existing data may be prepared for the purpose of Regulatory submission after the completion of Part A and completion of at least 4 subjects in each cohort of Part B. Detailed methodology for the interim report will be included in an SAP amendment, as appropriate, prior to the conduct of any interim analysis.

As this is an open label study, the Sponsor may also conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose adjustment decisions, facilitating pharmacokinetic (PK)/pharmacodynamic (PD) modeling, and/or to support clinical development.

7.3. Data Monitoring Committee

This study will use an external data monitoring committee (E-DMC).

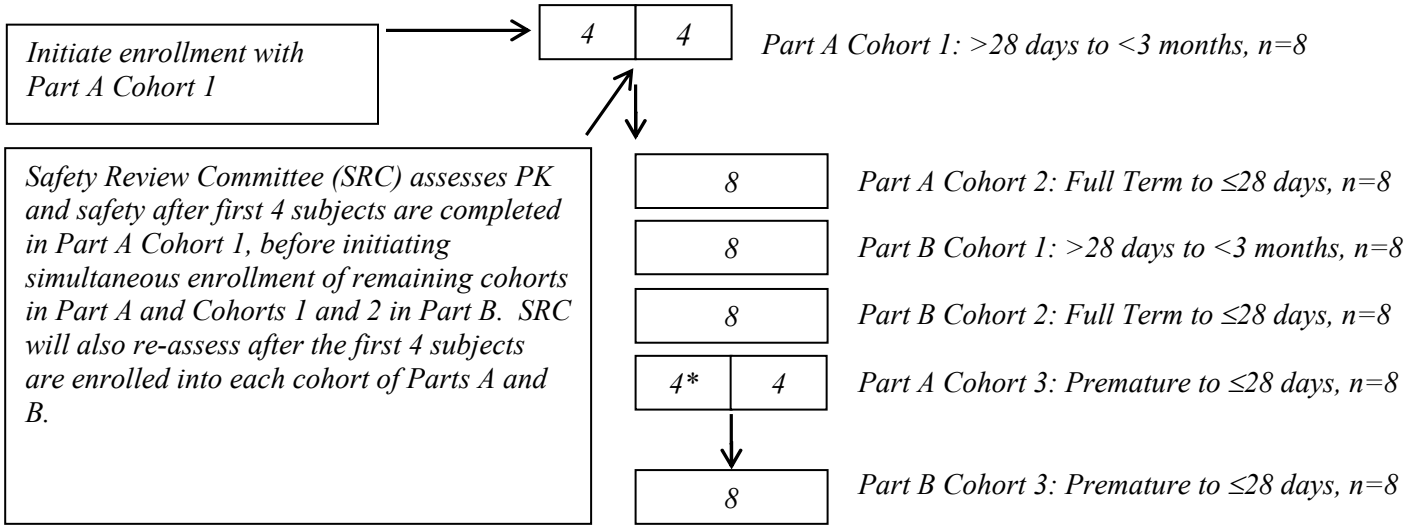
The E-DMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

7.4. Safety Review Committee

A Safety Review Committee (SRC) consisting 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 will assess PK, safety and tolerability from each cohort. 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.

The SRC will assess PK and safety data after the first 4 subjects are completed in Part A Cohort 1, before initiating simultaneous enrollment of remaining cohorts in Part A and Cohorts 1 and 2 in Part B. SRC will also re-assess after the first 4 subjects are enrolled into each cohort of Parts A and B. The SRC will assess the PK, safety and toleration of CAZ-AVI after the first 4 subjects are completed in Part A Cohort 3, before initiating enrollment in Part B Cohort 3. The sequence of cohort startup is provided in Figure 3.

Figure 3. Cohort Start Up



**The SRC will assess the PK, safety and toleration of CAZ AVI after the first 4 subjects are completed in Part A Cohort 3, before initiating enrollment in Part B Cohort 3.*

8. APPENDICES

Appendix 1. List of Microorganisms Considered to be Pathogens

Name of microorganism	Pathogen	Classification	Enterobacteriaceae
ACIDAMINOCOCCUS	No	Anaerobe	
ACINETOBACTER	No	Gram-neg	
ACINETOBACTER ANITRATUS	No	Gram-neg	
ACINETOBACTER CALCOACETICUS-BAUMANNII COMPLEX	No	Gram-neg	
ACINETOBACTER JOHNSONII	No	Gram-neg	
ACINETOBACTER LWOFFII	No	Gram-neg	
ACTINOMYCES	No	Anaerobe	
ACTINOMYCES MEYERII	No	Anaerobe	
ACTINOMYCES NAESLUNDII	No	Anaerobe	
ACTINOMYCES ODONTOLYTICUS	No	Anaerobe	
ACTINOMYCES TURICENSIS	No	Anaerobe	
AEROBIC GRAM-POSITIVE BACILLUS	No	Gram-pos	
AEROCOCCUS VIRIDANS	No	Gram-pos	
AEROMONAS	No	Gram-neg	
AEROMONAS HYDROPHILA	No	Gram-neg	
AEROMONAS HYDROPHILA COMPLEX	No	Gram-neg	
AEROMONAS PUNCTATA	No	Gram-neg	
AEROMONAS SOBRIA	No	Gram-neg	
AEROMONAS VERONII	No	Gram-neg	
ALCALIGENES	No	Gram-neg	
ANAEROBIC BACTERIA	No	Anaerobe	
ANAEROBIC COCCUS	No	Anaerobe	
ANAEROBIC GRAM-NEGATIVE BACILLUS	No	Anaerobe	
ANAEROBIC GRAM-NEGATIVE COCCUS	No	Anaerobe	
ANAEROBIC GRAM-POSITIVE BACILLUS	No	Anaerobe	
ANAEROBIC GRAM-POSITIVE COCCUS	No	Anaerobe	
ANAEROCOCCUS PREVOTII	No	Anaerobe	
ANAEROCOCCUS TETRADIUS	No	Anaerobe	
ARCANOBACTERIUM HAEMOLYTICUM	No	Gram-pos	
ARTHROBACTER	No	Gram-pos	
ARTHROBACTER CUMMINSII	No	Gram-pos	
ATOPOBIUM RIMAE	No	Anaerobe	
BACILLUS CEREUS	No	Gram-pos	
BACILLUS MEGATERIUM	No	Gram-pos	
BACILLUS SPECIES NOT ANTHRACIS	No	Gram-pos	
BACTEROIDES	No	Anaerobe	
BACTEROIDES CACCAE	No	Anaerobe	
BACTEROIDES CAPILLOSUS	No	Anaerobe	
BACTEROIDES DOREI	No	Anaerobe	
BACTEROIDES FAECIS	No	Anaerobe	
BACTEROIDES FRAGILIS	No	Anaerobe	
BACTEROIDES FRAGILIS GROUP	No	Anaerobe	
BACTEROIDES NORDII	No	Anaerobe	
BACTEROIDES OVATUS	No	Anaerobe	
BACTEROIDES STERCORIS	No	Anaerobe	
BACTEROIDES THETAIOTAOMICRON	No	Anaerobe	
BACTEROIDES UNIFORMIS	No	Anaerobe	
BACTEROIDES VULGATUS	No	Anaerobe	
BETA STREPTOCOCCUS, GROUP C	No	Gram-pos	
BETA STREPTOCOCCUS, GROUP F	No	Gram-pos	
BETA STREPTOCOCCUS, GROUP G	No	Gram-pos	
BIFIDOBACTERIUM	No	Anaerobe	
BIFIDOBACTERIUM ADOLESCENTIS	No	Anaerobe	
BIFIDOBACTERIUM BIFIDUM	No	Anaerobe	
BIFIDOBACTERIUM LONGUM	No	Anaerobe	
BIFIDOBACTERIUM PSEUDOCATENULATUM	No	Anaerobe	
BREVIBACTERIUM	No	Gram-pos	
BREVUNDIMONAS VESICULARIS	No	Gram-neg	
BURKHOLDERIA	No	Gram-neg	
BURKHOLDERIA CEPACIA	No	Gram-neg	
BURKHOLDERIA CEPACIA COMPLEX	No	Gram-neg	
CANDIDA	No		
CANDIDA ALBICANS	No		
CANDIDA DUBLINIENSIS	No		
CANDIDA GLABRATA	No		
CANDIDA KRUSEI	No		
CANDIDA PARAPSILOSIS	No		
CANDIDA SPECIES NOT ALBICANS	No		
CANDIDA TROPICALIS	No		
CAPNOCYTOPHAGA OCHRACEA	No	Gram-neg	
CHRYSEOBACTERIUM INDOLOGENES	No	Gram-neg	
CITROBACTER	Yes	Gram-neg	E
CITROBACTER AMALONATICUS	Yes	Gram-neg	E
CITROBACTER BRAAKII	Yes	Gram-neg	E
CITROBACTER FREUNDII	Yes	Gram-neg	E
CITROBACTER FREUNDII COMPLEX	Yes	Gram-neg	E
CITROBACTER KOSERI	Yes	Gram-neg	E
CITROBACTER YOUNGAE	Yes	Gram-neg	E
CLOSTRIDIUM	No	Anaerobe	
CLOSTRIDIUM ALDENENSE	No	Anaerobe	
CLOSTRIDIUM BARATII	No	Anaerobe	
CLOSTRIDIUM BUTYRICUM	No	Anaerobe	
CLOSTRIDIUM CLOSTRIDIOFORME	No	Anaerobe	
CLOSTRIDIUM DIFFICILE	No	Anaerobe	

Name of microorganism	Pathogen	Classification	Enterobacteriaceae
CLOSTRIDIUM DISPORICUM	No	Anaerobe	
CLOSTRIDIUM GLYCOLICUM	No	Anaerobe	
CLOSTRIDIUM HATHEWAYI	No	Anaerobe	
CLOSTRIDIUM HISTOLYTICUM	No	Anaerobe	
CLOSTRIDIUM INNOCUUM	No	Anaerobe	
CLOSTRIDIUM PERFRINGENS	No	Anaerobe	
CLOSTRIDIUM RAMOSUM	No	Anaerobe	
CLOSTRIDIUM SEPTICUM	No	Anaerobe	
CLOSTRIDIUM SPOROGENES	No	Anaerobe	
CLOSTRIDIUM SYMBIOSUM	No	Anaerobe	
CLOSTRIDIUM TERTIUM	No	Anaerobe	
COAGULASE NEGATIVE STAPHYLOCOCCUS	No	Gram-pos	
COLLINSELLA AEROFACIENS	No	Anaerobe	
COMAMONAS KERSTERSII	No	Gram-neg	
COMAMONAS TESTOSTERONI	No	Gram-neg	
CORYNEBACTERIUM	No	Gram-pos	
CORYNEBACTERIUM GLUCURONOLYTICUM	No	Gram-pos	
CRONOBACTER SAKAZAKII	Yes	Gram-neg	E
DERMABACTER HOMINIS	No	Gram-pos	
DIALISTER PNEUMOSINTES	No	Anaerobe	
DIPHTHEROIDS	No	Gram-pos	
EDWARDSIELLA HOSHINAE	Yes	Gram-neg	E
EGGERTHELLA	No	Anaerobe	
EGGERTHELLA LENTA	No	Anaerobe	
EIKENELLA	No	Gram-neg	
EIKENELLA CORRODENS	No	Gram-neg	
ENTEROBACTER	Yes	Gram-neg	E
ENTEROBACTER AEROGENES	Yes	Gram-neg	E
ENTEROBACTER ASBURIAE	Yes	Gram-neg	E
ENTEROBACTER CLOACAE	Yes	Gram-neg	E
ENTEROCOCCUS	No	Gram-pos	
ENTEROCOCCUS AVIUM	No	Gram-pos	
ENTEROCOCCUS CASSELIFLAVUS	No	Gram-pos	
ENTEROCOCCUS DURANS	No	Gram-pos	
ENTEROCOCCUS FAECALIS	No	Gram-pos	
ENTEROCOCCUS FAECIUM	No	Gram-pos	
ENTEROCOCCUS GALLINARUM	No	Gram-pos	
ENTEROCOCCUS HIRAE	No	Gram-pos	
ENTEROCOCCUS RAFFINOSUS	No	Gram-pos	
ENTEROCOCCUS THAILANDICUS	No	Gram-pos	
ESCHERICHIA COLI	Yes	Gram-neg	E
EUBACTERIUM	No	Anaerobe	
EUBACTERIUM LIMOSUM	No	Anaerobe	
FINEGOLDIA MAGNA	No	Anaerobe	
FLAVOBACTERIUM	No	Gram-neg	
FUSOBACTERIUM	No	Anaerobe	
FUSOBACTERIUM MORTIFERUM	No	Anaerobe	

Name of microorganism	Pathogen	Classification	Enterobacteriaceae
FUSOBACTERIUM NAVIFORME	No	Anaerobe	
FUSOBACTERIUM NECROPHORUM	No	Anaerobe	
FUSOBACTERIUM NUCLEATUM	No	Anaerobe	
FUSOBACTERIUM VARIUM	No	Anaerobe	
GEMELLA HAEMOLYSANS	No	Gram-pos	
GEMELLA MORBILLORUM	No	Anaerobe	
GLOBICATELLA SANGUINIS	No	Gram-pos	
GRAM-NEGATIVE BACILLUS	No	Gram-neg	
GRAM-POSITIVE BACILLUS	No	Gram-pos	
GRAM-POSITIVE COCCUS	No	Gram-pos	
GRANULICATELLA ADIACENS	No	Gram-pos	
GRANULICATELLA ELEGANS	No	Gram-pos	
GROUP D NON-ENTEROCOCCAL STREPTOCOCCUS	No	Gram-pos	
HAEMOPHILUS INFLUENZAE	No	Gram-neg	
HAEMOPHILUS PARAINFLUENZAE	No	Gram-neg	
HAFNIA ALVEI	Yes	Gram-neg	E
KLEBSIELLA	Yes	Gram-neg	E
KLEBSIELLA OXYTOCA	Yes	Gram-neg	E
KLEBSIELLA OZAENAE	Yes	Gram-neg	E
KLEBSIELLA PNEUMONIAE	Yes	Gram-neg	E
KLUYVERA	Yes	Gram-neg	E
KLUYVERA ASCORBATA	Yes	Gram-neg	E
LACTOBACILLUS	No	Anaerobe	
LACTOBACILLUS FERMENTUM	No	Anaerobe	
LACTOBACILLUS GASSERI	No	Anaerobe	
LACTOBACILLUS PARACASEI	No	Anaerobe	
LACTOCOCCUS GARVIEAE	No	Anaerobe	
LACTOCOCCUS LACTIS	No	Anaerobe	
LEUCONOSTOC	No	Gram-pos	
LISTERIA	No	Gram-pos	
METHICILLIN RESIS. STAPHYLOCOCCUS AUREUS	No	Gram-pos	
MICROCOCCUS LUTEUS	No	Gram-pos	
MORGANELLA MORGANII	Yes	Gram-neg	E
NEISSERIA CINEREA	No	Gram-neg	
NON-FERMENTATIVE GRAM-NEGATIVE BACILLUS	No	Gram-neg	
PANTOEA	Yes	Gram-neg	E
PANTOEA AGGLOMERANS	Yes	Gram-neg	E
PARABACTEROIDES	No	Anaerobe	
PARABACTEROIDES DISTASONIS	No	Anaerobe	
PARABACTEROIDES JOHNSONII	No	Anaerobe	
PARABACTEROIDES MERDAE	No	Anaerobe	
PARVIMONAS MICRA	No	Anaerobe	
PASTEURELLA MULTOCIDA	No	Gram-neg	
PEPTONIPHILUS	No	Anaerobe	
PEPTONIPHILUS ASACCHAROLYTICUS	No	Anaerobe	
PEPTONIPHILUS HAREI	No	Anaerobe	
PEPTOSTREPTOCOCCUS	No	Anaerobe	

Name of microorganism	Pathogen	Classification	Enterobacteriaceae
PEPTOSTREPTOCOCCUS ANAEROBIUS	No	Anaerobe	
PEPTOSTREPTOCOCCUS STOMATIS	No	Anaerobe	
PHOTOBACTERIUM DAMSELAE	No	Gram-neg	
PORPHYROMONAS	No	Anaerobe	
PORPHYROMONAS GINGIVALIS	No	Anaerobe	
PREVOTELLA	No	Anaerobe	
PREVOTELLA BARONIAE	No	Anaerobe	
PREVOTELLA BIVIA	No	Anaerobe	
PREVOTELLA BUCCAE	No	Anaerobe	
PREVOTELLA BUCCALIS	No	Anaerobe	
PREVOTELLA DENTICOLA	No	Anaerobe	
PREVOTELLA HEPARINOLYTICA	No	Anaerobe	
PREVOTELLA INTERMEDIA	No	Anaerobe	
PREVOTELLA LOESCHEII	No	Anaerobe	
PREVOTELLA MELANINOGENICA	No	Anaerobe	
PREVOTELLA NIGRESCENS	No	Anaerobe	
PREVOTELLA ORALIS	No	Anaerobe	
PROPIONIBACTERIUM ACNES	No	Anaerobe	
PROPIONIBACTERIUM PROPIONICUM	No	Anaerobe	
PROTEUS	Yes	Gram-neg	E
PROTEUS MIRABILIS	Yes	Gram-neg	E
PROTEUS RETTGERI	Yes	Gram-neg	E
PROTEUS VULGARIS	Yes	Gram-neg	E
PROTEUS VULGARIS GROUP	Yes	Gram-neg	E
PROVIDENCIA	Yes	Gram-neg	E
PSEUDOMONAS	No	Gram-neg	
PSEUDOMONAS AERUGINOSA	Yes	Gram-neg	
PSEUDOMONAS ALCALIGENES	No	Gram-neg	
PSEUDOMONAS FLUORESCENS	No	Gram-neg	
PSEUDOMONAS MENDOCINA	No	Gram-neg	
PSEUDOMONAS PUTIDA	No	Gram-neg	
PSEUDOMONAS STUTZERI	No	Gram-neg	
RAOULTELLA ORNITHINOLYTICA	Yes	Gram-neg	E
RAOULTELLA PLANTICOLA	Yes	Gram-neg	E
ROTHIA DENTOCARIOSA	No	Gram-pos	
RUMINOCOCCUS GNAVUS	No	Anaerobe	
SALMONELLA SEROTYPE ENTERITIDIS	Yes	Gram-neg	E
SERRATIA MARCESCENS	Yes	Gram-neg	E
SHEWANELLA ALGAE	No	Gram-neg	
SHIGELLA DYSENTERIAE	Yes	Gram-neg	E
SLACKIA EXIGUA	No	Anaerobe	
SOLOBACTERIUM MOOREI	No	Anaerobe	

Name of microorganism	Pathogen	Classification	Enterobacteriaceae
STAPHYLOCOCCUS	No	Gram-pos	
STAPHYLOCOCCUS AUREUS	No	Gram-pos	
STAPHYLOCOCCUS CAPITIS	No	Gram-pos	
STAPHYLOCOCCUS COHNII	No	Gram-pos	
STAPHYLOCOCCUS EPIDERMIDIS	No	Gram-pos	
STAPHYLOCOCCUS HAEMOLYTICUS	No	Gram-pos	
STAPHYLOCOCCUS HOMINIS	No	Gram-pos	
STAPHYLOCOCCUS SAPROPHYTICUS	No	Gram-pos	
STAPHYLOCOCCUS WARNERI	No	Gram-pos	
STENOTROPHOMONAS MALTOPHILIA	No	Gram-neg	
STREPTOCOCCUS	No	Gram-pos	
STREPTOCOCCUS ACIDOMINIMUS	No	Gram-pos	
STREPTOCOCCUS AGALACTIAE	No	Gram-pos	
STREPTOCOCCUS ALPHA-HEMOLYTIC	No	Gram-pos	
STREPTOCOCCUS ANGINOSIS	No	Gram-pos	
STREPTOCOCCUS ANGINOSUS GROUP	No	Gram-pos	
STREPTOCOCCUS ANGINOSUS-CONSTELLATUS	No	Gram-pos	
STREPTOCOCCUS BETA-HEMOLYTIC	No	Gram-pos	
STREPTOCOCCUS BOVIS	No	Gram-pos	
STREPTOCOCCUS BOVIS GROUP	No	Gram-pos	
STREPTOCOCCUS CANIS	No	Gram-pos	
STREPTOCOCCUS CONSTELLATUS	No	Gram-pos	
STREPTOCOCCUS CRISTATUS	No	Gram-pos	
STREPTOCOCCUS DYSGALACTIAE SUBSP. EQUISIMILIS	No	Gram-pos	
STREPTOCOCCUS EQUINUS	No	Gram-pos	
STREPTOCOCCUS GALLOLYTICUS	No	Gram-pos	
STREPTOCOCCUS GROUP C	No	Gram-pos	
STREPTOCOCCUS INTERMEDIUS	No	Gram-pos	
STREPTOCOCCUS MILLERI	No	Gram-pos	
STREPTOCOCCUS MITIS	No	Gram-pos	
STREPTOCOCCUS MITIS GROUP	No	Gram-pos	
STREPTOCOCCUS MUTANS	No	Gram-pos	
STREPTOCOCCUS ORALIS	No	Gram-pos	
STREPTOCOCCUS PARASANGUINIS	No	Gram-pos	
STREPTOCOCCUS PNEUMONIAE	No	Gram-pos	
STREPTOCOCCUS PYOGENES	No	Gram-pos	
STREPTOCOCCUS SALIVARIUS	No	Gram-pos	
STREPTOCOCCUS SALIVARIUS GROUP	No	Gram-pos	
STREPTOCOCCUS SANGUINIS	No	Gram-pos	
STREPTOCOCCUS VIRIDANS	No	Gram-pos	
STREPTOCOCCUS VIRIDANS GROUP	No	Gram-pos	
VEILLONELLA	No	Anaerobe	

This list will be reviewed by microbiologist and finalized prior to database lock.

Appendix 2. Imputation of Incomplete Date of Birth and Derivation of Age

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 incomplete DOB, date of informed consent, expected age in days for each cohort.

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 in the date of informed consent and the expected age in days 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 by subtracting the imputed DOB from the date of informed consent.

Notes:

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, if a term infant from Cohort 1 has an incomplete DOB of Aug2018, and the date of informed consent of 18Aug2018 the ranges of plausible values described in Steps 1 and 2 are Range 1: 01Aug2018 to 31Aug2018, and Range 2: 18May2018 to 20Jul2018. Since these two ranges of plausible DOBs are not overlapping, the range of possible DOBs in Step 3 will be determined using the range from Step 1 (01 to 31Aug2018) and the date of informed consent (18Aug2018), ie, 01Aug2018 to 18Aug2018. In this case the imputed DOB is 09Aug2018, therefore the derived age is 9 days.

Table 6. **Expected Age for Each Cohort**

Cohort	Definition	Expected age for Cohort
1	Term infants age >28 days to <89 days or Pre-term infants with corrected age >28 days to <89 days	From 29 to 88 days The expected ages will depend on the corrected age (CA), and the gestational age (GA), where CA = Age - (40 – GA) X 7, which is equivalent to Age = CA + (40 - GA) X 7 For example, for pre-term neonates with GA=30 weeks the interval for CA of 29 to 88 days correspond to an interval for the chronological age of 99 to 158 days, which represent the expected ages of pre-term infants in Cohort 1.
2	Term neonates from birth to <= 28 days	From birth to 28 days
3	Pre-term neonates from birth to <= 28 days	From birth to 28 days

GA = Gestational Age, the time elapsed between the first day of the last menstrual period and birth;

Corrected age is the age of the infant from the expected date of delivery, calculated by subtracting the number of weeks born before 40 weeks of gestation from the chronological age. Corrected age (weeks) = chronological age in weeks – (40 – gestational age in weeks). See Appendix 2 of protocol for calculation of corrected age in days and alternative perinatal age terminologies.