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

Investigational Product Number:	PF-06947386
Investigational Product Name:	Zavicefta (Ceftazidime-Avibactam)
United States (US) Investigational New Drug (IND) Number:	101,307
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Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 1	27 June 2019	In addition to minor administrative changes and clarifications, protocol amendment 1 includes the following: Throughout the document, changes were made to recording of temperature measurement post-baseline. Recording of temperature will not be performed postdose as originally indicated. The protocol summary, the introduction and study design have been updated to include the CAZ-AVI pediatric approval in children from 3 months of age and older in 2019 received in the US for the treatment of cIAI (when combined with metronidazole), and for the treatment of cUTI. Text now also has been updated to show that CAZ-AVI has received regulatory approval in 51 countries worldwide. Text has been updated to show that this study is planned to be performed at approximately 40 sites and 15 countries in the US, Europe, and Asia. Part B Cohort 3 enrollment sequence has been revised as requested by the EMA Pediatric Committee (PDCO) on 19 Oct 2018. The purpose of this request was to ensure that enrollment of subjects in Part B Cohort 3, who represent the most vulnerable population based on their age (Pre term neonates (GA ≥26 to <37 weeks) from birth to ≤28 days), is initiated only after data from the other cohorts is first evaluated. PK analyses will be performed as described in Section 9.2 Pharmacokinetic Analysis so the description of PK endpoints in Section 2 was simplified. Another secondary endpoint for Part B (emergent infections) has been added. Text was updated in Sections 7.1.1 and 9.2 to use 'nominal sampling time' uniformly throughout the protocol in the description of the pharmacokinetic endpoint, for consistency with the endpoint description Section 2. Inclusion criteria text in Section 4.1.1 for all subjects (criterion 3a) has been revised to clarify that <3 months is <89 days. It has also been clarified in Section 4.1.3 (criterion 2) 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 enrolled.

Document	Version Date	Summary of Changes and Rationale
		The Table 2 title in Section 5.5 was simplified and the term "dose" has been revised to "weight-based dose". The Infusion Volume in Table 2, Section 5.5 and the requirement for using aseptic technique for study drug preparation and administration in Section 5.4.2 has also been revised to match the Investigational Product Manual. The following sentence has been added to the Concomitant Treatments section: "In Part A, the use of any other antibiotics is permitted, including other antibiotics combined with beta lactamase inhibitors. In Part B, the use of antibiotics combined with other beta lactamase inhibitors is prohibited, including combinations with the beta lactamase inhibitors sulbactam, tazobactam, clavulanate, and any new beta lactamase inhibitors which become available during the course of the study." Custom blue top tubes will be used to collect plasma for PK analysis instead of the standard sodium fluoride/potassium oxalate grey-top tube. Additional details have been provided regarding sources of blood for PK blood samples, including multi-lumen catheters where one lumen is used to infuse CAZ-AVI. The collection time of the first blood PK samples has been changed to indicate that it should be collected anytime within 15 minutes after stopping CAZ-AVI infusion. The paragraph about PK sample collection in Part B has been revised to clarify that in Part B, PK samples will be collected after at least 3 consecutive doses of CAZ-AVI have been infused. The definition of PK sampling times relative to the start of the infusion has been added to explain the nominal times for PK samples as specified in the CRF. Additional possible uses specified for left over plasma, if any, not used for PK assessments. It has been clarified that in Part B, the PK analysis set consist of all subjects with at least 3 consecutive doses of CAZ-AVI in Part B with at least 1 ceftazidime and/or avibactam plasma PK measurement available. In the efficacy analysis Section 9.4, the definition of ITT, a sentence detailing the summary of all-cause mortality, a clarification that clinical outcomes will be summarized for all 3 analysis sets (ITT, MITT and micro ITT), and a clarification

Document	Version Date	Summary of Changes and Rationale
		that microbiological response will be summarized only for the micro ITT, have been added. A Per-subject microbiological Response table (Table 7) has been added to section 9.4.2 as well as the definition of emergent infections (Table 8). Appendix 2 was added to clarify the determination of pre-term infant eligibility for Cohort 1 according to corrected age. The original Appendix 2 was moved to Appendix 3.
Original protocol	11 July 2018	Not applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs/ethics committees (ECs).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

PROTOCOL SUMMARY

Background and Rationale

Ceftazidime is an injectable third generation cephalosporin antibiotic which has been in clinical use worldwide for more than 25 years for the treatment of infections caused by aerobic Gram-negative pathogens. Ceftazidime has been shown to be safe and effective in adult and pediatric patients (neonates to adolescents <18 years of age) for a range of indications. However, over the past 15 years, resistance to ceftazidime has been increasing worldwide. The most common mechanism of resistance is bacterial production of β-lactamases, in particular, extended spectrum β-lactamases (ESBLs).

In order to counter ceftazidime resistance and restore antibacterial activity to ceftazidime, a combination product has been developed in which ceftazidime is combined with avibactam, a novel non-β-lactam β-lactamase inhibitor. Although avibactam itself possesses no intrinsic antibacterial activity, it has been shown to restore activity of ceftazidime against clinically relevant β-lactamases of Class A and Class C varieties, including extended spectrum β-lactamases (ESBLs) and serine-based *Klebsiella pneumoniae* carbapenemases (KPCs) and AmpC producing strains. Although avibactam has no inhibitory effect on Class B metallo-β-lactamases, it does inhibit the activity of some Class D β-lactamases (eg, OXA-48 type carbapenemase). A fixed dose combination of ceftazidime and avibactam (CAZ-AVI) was approved for use in adults in the United States in 2015, and for use in children three months of age and older in 2019 for complicated intra-abdominal infection (cIAI) (in combination with metronidazole) and complicated urinary tract infection (cUTI), under the brand name AVYCAZ.[1] A fixed dose combination of ceftazidime and avibactam (CAZ-AVI) was approved for use in adults in Europe in 2016 under the brand name Zavicefta.[2] This fixed-dose combination of CAZ-AVI is currently being evaluated globally for pediatric use in hospital-acquired pneumonia/ventilator associated pneumonia (HAP/VAP).

Study Sites and Number of Subjects Planned

This study is planned to be performed at approximately 40 sites and 15 countries in the United States (US), Europe, and Asia.

The study will be conducted in 2 parts, Part A and Part B. Part A is a non-randomized open-label single-dose pharmacokinetic (PK) study enrolling at least 24 neonates and infants from 26 weeks gestational age (GA) to <3 months of age who are hospitalized and receiving other intravenous antibiotics for suspected or confirmed bacterial infection. Part B is a non-randomized open-label, multi-dose, single treatment arm PK study enrolling at least 24 neonates and infants from 26 weeks GA to <3 month of age who are hospitalized with suspected or confirmed aerobic Gram-negative bacterial infections (excluding central nervous system infections) requiring intravenous antibiotic therapy.

Parts A and B will each be divided into 3 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

*The number of pre-term corrected age infants in Cohort 1 is limited to 3 each in Parts A and B. Sites will be notified in writing if this limit is reached.

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 (Engle, 2004).[3] Corrected age (weeks) = chronological age in weeks – (40 – gestational age in weeks). See Appendix 2 for calculation of corrected age in days and alternative perinatal age terminologies.

Enrollment for this study will begin with Cohort 1 of Part A. 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 delegates will assess the PK, safety and toleration of CAZ-AVI in the first 4 subjects in Cohort 1 of Part A prior to initiating simultaneous enrollment of the remaining cohorts in Part A and Cohorts 1 and 2 in Part B. Based on this assessment the SRC in conjunction with the external data monitoring committee (E-DMC) may recommend a dose adjustment from Appendix 3 and/or a modified enrollment sequence which will be communicated to the study sites in a written protocol Clarification Memorandum and incorporated into the next protocol version. A similar assessment will be conducted after the first 4 subjects are enrolled into each cohort of Part A and Part B. Enrollment will not begin in Cohort 3 of Part B until the SRC has conducted its review of the first 4 subjects in Cohort 3 of Part A. If CAZ-AVI safety, toleration or PK are not consistent with expectations after the first 4 subjects in any Cohort then it may be necessary to delay or stagger the remaining cohorts to gain more experience, in which case an updated Pfizer and EDMC approved cohort enrollment sequence will be provided to sites in a written protocol Clarification Memorandum.

Objectives and Endpoints

Part A Primary Objective:	**Part A Primary Endpoints:**
To characterize the pharmacokinetics of a single intravenous dose of ceftazidime-avibactam in hospitalized neonates and infants from birth to <3 months.	CAZ and AVI plasma concentrations by nominal sampling time.
Part A Secondary Objective:	**Part A Secondary Endpoint:**
To evaluate the safety and tolerability of a single intravenous dose of ceftazidime-avibactam in hospitalized neonates and infants from birth to <3 months.	Safety and tolerability endpoints include adverse events, serious adverse events, deaths, discontinuations due to adverse events and laboratory abnormalities.

Part B Primary Objective:	**Part B Primary Endpoint:**
To evaluate the safety and tolerability of ceftazidime-avibactam for the treatment of aerobic Gram-negative infection in neonates and infants from birth to <3 months.	Safety and tolerability endpoints include adverse events, serious adverse events, deaths, discontinuations due to adverse events and laboratory abnormalities.
Part B Secondary Objectives:	**Part B Secondary Endpoints:**
To evaluate the pharmacokinetic profile of multiple intravenous doses of ceftazidime-avibactam in hospitalized neonates and infants from birth to <3 months.	CAZ and AVI plasma concentrations by nominal sampling time.
To evaluate the efficacy of ceftazidime-avibactam for the treatment of aerobic Gram-negative infection in neonates and infants from birth to <3 months.	Efficacy outcome measures will include: • All-cause mortality. • Clinical outcome at End-of-Intravenous, End-of-Treatment, Test-of-Cure and Late Follow-Up. • Cure defined as clinical improvement and no need for further antibiotic treatment, 7 to 14 days after end of treatment. • Microbiological eradication 7 to 14 days after end of treatment (micro-Intent-to-Treat analysis set). • Emergent infections.

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 assessed as a secondary objective in the multi-dose portion of the trial.

In Part A subjects will have a Screening visit (Visit 1), a Baseline visit (Visit 2) during which they will receive a single intravenous (IV) infusion of CAZ-AVI followed by timed PK assessments, and then 2 follow-up assessments at 24 and 48 hours after the start of the infusion, and a Late Follow-up assessment 28-35 days after the infusion. In Part B, subjects will have a Screening visit (Visit 1), a Baseline visit (Visit 2) during which they will start IV treatment with CAZ-AVI, and then ongoing treatment for 2-14 days (with an optional switch to alternative oral therapy or outpatient parenteral antimicrobial therapy (OPAT) with another IV antibiotic after at least 48 hours of IV CAZ-AVI, an End-of-Intravenous (EOIV) Treatment assessment within 24 hours after the last IV infusion of CAZ-AVI, and End-of-Treatment (EOT) assessment within 48 hours after the last oral or OPAT treatment (if applicable), a Test-of-Cure (TOC) assessment 7-14 days after the last dose of any drug (IV or oral) and a Late Follow-Up (LFU) assessment 28-35 days after the last IV infusion of CAZ-AVI.

For Part A and Part B, three single PK blood samples, each 0.3 mL, (2 x 0.3 mL for premature infants weighing less than 1 kg) will be obtained during the 6 hours following the infusion. For Part A, PK samples will be collected after a single dose of CAZ-AVI has been infused. For Part B, the PK samples will be collected after at least 3 consecutive doses of CAZ-AVI have been infused.

Each subject is expected to complete the study, including the Late Follow-Up visit. Participants in the study must be inpatients at the study site institution to receive study medication, however an optional switch to alternative oral therapy or OPAT after at least 48 hours of CAZ-AVI is permitted in Part B with subsequent hospital discharge if appropriate. Subjects who are not evaluable for PK will be replaced. An evaluable subject is one who has received a single IV dose of CAZ-AVI in Part A or at least 3 consecutive doses of CAZ-AVI in Part B and has at least 1 ceftazidime and/or avibactam plasma measurement available.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The Investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Part A Schedule of Activities

Protocol Activity	Screening[a]	Baseline/ IV Infusion	24 hr Assessment	48 hr Assessment	Late Follow-Up (LFU)[b]
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Study Day	**Days -1 to 1**	**Day 1**	**Day 2**	**Day 3**	**Day 28-35**
Clinic Assessments					
Informed consent	X				
Inclusion/Exclusion criteria	X				
Demography	X				
Medical history (including pre- and post-birth)	X				
Physical examination	X	X	X	X	
Length	X				
Weight (first weight of the day)	X	X	X	X	
Vital signs evaluation[c]	X[d]	X	X	X	
Oxygen saturation (if available)	X	X	X	X	
Serious and Non-Serious Adverse event assessment	X	X	X	X	X
Adjunctive therapeutic procedures (if any)		X	X	X	
CXR, CT scan, or other imaging tests	X[e]		X[f]		
Laboratory Assessments[g]					
Hematology[h]	X	X[f]	X	X[f]	
Blood chemistry[h]	X	X[f]	X	X[f]	
Urinalysis[h]	X	X[f]	X	X[f]	
Urine output[i]	X	X	X		
Study Medication					
CAZ-AVI Infusion		X			
Pharmacokinetic (PK) blood sampling[j]		X			

Protocol Activity	Screening[a]	Baseline/ IV Infusion	24 hr Assessment	48 hr Assessment	Late Follow-Up (LFU)[b]
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Study Day	**Days -1 to 1**	**Day 1**	**Day 2**	**Day 3**	**Day 28-35**
Concomitant Treatment[k]	X	X	X	X	

Abbreviations: CAZ-AVI = ceftazidime-avibactam; CT scan = computed tomography scan; CXR = chest x-ray; PK = Pharmacokinetic.

a. Screening assessments can serve as baseline if they are completed on the same calendar day as Day 1, prior to CAZ-AVI infusion, but they must be completed no earlier than the day before the start of CAZ-AVI infusion (except for laboratory assessments which may be up to 2 days before the start of CAZ-AVI infusion, as noted in footnote g). If additional assessments are conducted per standard of care prior to the first infusion of CAZ-AVI the assessments closest to the infusion will be considered baseline.

b. The Late Follow-up (LFU) visit to capture any potential adverse events or serious adverse may be conducted by telephone.

c. Vital signs (blood pressure, heart rate/pulse, respiratory rate and temperature). Post-baseline, record the daily highest and lowest temperature measurements. Additional vitals may be taken as needed.

d. Record at least 2 heart rate/pulse measurements taken during a 30 minute period. Record at least 2 blood pressure measurements, or record highest and lowest measurements if continuously monitored, over a 30 minute period.

e. At screening, obtain results of CXR, CT scan, or other imaging tests (eg, echocardiogram, CT scan, magnetic resonance imaging (MRI), ultrasound) if performed as part of the subject's regular medical care up to 3 days before screening.

f. If clinically indicated and performed as part of subject's regular medical care.

g. If the subject is improving and laboratory assessments were performed within 2 days of CAZ-AVI infusion, those test results may be used for eligibility and they do not need to be repeated for screening.

h. Refer to Section 7.4.1 for list of tests.

i. For subjects who have been hospitalized for ≥8 hours, calculate urine output over the last 8 hour period.

j. Blood samples for PK (0.3 mL per sample) will be collected on Day 1 following IV infusion of CAZ-AVI, at the following time points: 1) anytime within 15 minutes after stopping CAZ-AVI infusion, 2) anytime between 30 minutes and 90 minutes after stopping CAZ-AVI infusion, and 3) anytime between 300 minutes (5 hours) and 360 minutes (6 hours) after stopping CAZ-AVI infusion. If the dosing interval for any cohort is increased from every 8 hour to every 12 hours, then timing of the third PK sample will be changed to anytime between 540 minutes (9 hours) and 600 minutes (10 hours) after stopping CAZ-AVI infusion. Preference should be given to the first and third collection time if only two PK samples are obtained for any reason. For infants weighing less than 1 kg only the first and third PK blood sample will be collected. PK blood samples are NOT to be drawn if the subject received a blood or blood component transfusion within the past 24 hours. For subjects who are at risk from additional blood loss, collection of PK samples will require assessment by the Investigator.

k. Review and record prior and concomitant medications taken or received within 7 days before the first dose of study therapy, including, but not limited to, all antimicrobials, parenteral nutrition, and blood and blood component transfusions. For 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.

Part B Schedule of Activities

Protocol Activity	Screening[a]	Baseline/1st IV Infusion	Treatment	End of IV Treatment[b]	End of Treatment[c]	Test of Cure[d]	Late Follow-Up[e]
Visit Number	**Visit 1**	**Visit 2**	**Visits 3 to 15**	**Visit 16**	**Visit 17**	**Visit 18**	**Visit 19**
Study Day[a]	**Days -1 to 1**	**Day 1**	**Days 2 to 14**	**≤24 hr after last IV infusion**	**≤48 hr after last drug dose**	**7-14 Days after last drug dose**	**28-35 days after last CAZ-AVI infusion**
Clinic Assessments							
Informed consent	X						
Inclusion/Exclusion criteria	X						
Demography	X						
Medical history (including pre- and post-birth)	X						
Microbiological/Infectious history[f]	X						
Physical examination	X	X	X	X	X	X	X
Length	X						
Weight (first weight of the day)	X	X	X	X	X	X	X
Vital signs evaluation[g]	X[h]	X	X	X	X	X	X
Oxygen saturation (if available)	X	X	X	X	X	X	X
Serious and Non-Serious Adverse event assessment	X	X	X	X	X	X	X
Clinical outcome				X	X	X	X
Adjunctive therapeutic procedures (if any)		X	X	X	X	X	X
CXR, CT scan, or other imaging tests	X[i]			X[j]			
Laboratory assessments							
Hematology[k]	X	X[j]		X	X[j]		X[j]
Blood chemistry[k]	X	X[j]		X	X[j]		X[j]
Base excess			X[j]				
CRP and Procalcitonin[k]			X[j]				
Urinalysis[k]	X	X[j]		X	X[j]		X[j]
Urine output	X[l]	X	X	X	X[j]		
Study Medication							
CAZ-AVI Infusion		X	X[m]				

Protocol Activity	**Screening[a]**	**Baseline/1st IV Infusion**	**Treatment**	**End of IV Treatment[b]**	**End of Treatment[c]**	**Test of Cure[d]**	**Late Follow-Up[e]**
Visit Number	**Visit 1**	**Visit 2**	**Visits 3 to 15**	**Visit 16**	**Visit 17**	**Visit 18**	**Visit 19**
Study Day[a]	**Days -1 to 1**	**Day 1**	**Days 2 to 14**	**≤24 hr after last IV infusion**	**≤48 hr after last drug dose**	**7-14 Days after last drug dose**	**28-35 days after last CAZ-AVI infusion**
Pharmacokinetic (PK) blood sampling[n]			X				
Concomitant Treatment[o]	X	X	X	X	X	X	X
Microbiology[p]							
Blood Culture	X[l]						
Urine Culture	X[l]						
Other specimen or tissue culture	X[l]						

Abbreviations: CAZ-AVI = ceftazidime-avibactam; CRP = C-Reactive Protein; CT scan = computed tomography scan; CXR = chest x-ray; IV = Intravenous.

a. Screening assessments can serve as baseline if they are completed on the same calendar day as Day 1, prior to CAZ-AVI infusion, but they must be completed no earlier than the day before the start of CAZ-AVI infusion. If additional assessments are conducted per standard of care prior to the first infusion of CAZ-AVI the assessments closest to the infusion will be considered baseline.

b. Perform End of IV Treatment (EOIV) assessments within 24 hours after completion of the last infusion of CAZ-AVI or at time of premature discontinuation of CAZ-AVI or early withdrawal from the study. A switch to oral antibacterial therapy or outpatient parenteral antimicrobial therapy (OPAT) may be performed at Investigator discretion after at least 48 hours of IV CAZ-AVI therapy. EOIV assessments must occur before starting oral or OPAT switch therapy. If subjects are discharged from the hospital after a switch to oral therapy or OPAT any remaining study visits may be conducted as outpatients.

c. Perform End of Treatment (EOT) assessments within 48 hours after the last dose of IV or oral antibacterial therapy, whichever comes later or at time of premature discontinuation of antibacterial therapy or early withdrawal from study. If there is no switch to oral antibacterial therapy or OPAT then EOIV is also EOT. If a subject was previously assessed as a clinical failure, only the safety assessments need to be performed (ie, AEs and SAEs, concomitant medications, adjunctive therapeutic procedures, weight, vital signs, CBC with differential and chemistry panel if clinically indicated and performed as part of subject's regular medical care).

d. Conduct Test of Cure (TOC) assessments 7 to 14 days after the last dose of antibacterial therapy (IV or oral). If a subject was previously assessed as a clinical failure, only the safety assessments need to be performed (ie, AEs and SAEs, concomitant medications, adjunctive therapeutic procedures, weight, vital signs, CBC with differential and chemistry panel if clinically indicated and performed as part of subject's regular medical care).

e. Conduct Late Follow-up (LFU) assessments, preferably in person 28 to 35 days after the last IV infusion of CAZ-AVI. The clinical outcome assessed at this visit is for relapse or potential re-infection. The LFU may be conducted via telephone for any subject who has not experienced clinical relapse, did not have ongoing AEs or SAEs at TOC, or did not develop AEs or SAEs since TOC. If symptoms of relapse or new AEs or SAEs are noted, or at the discretion of the Investigator, the subject should be immediately scheduled for an in-person visit. If the visit is in-person, weight, vital signs and oxygen saturation should be recorded. If a subject was previously assessed as a clinical failure, only the safety assessments need to be performed (ie, AEs and SAEs, concomitant medications, adjunctive therapeutic procedures, weight, vital signs, CBC with differential and chemistry panel if clinically indicated and performed as part of subject's regular medical care).

f. Obtain any prior microbiological and clinical data (eg, notes in medical records confirming worsening of signs and symptoms of infection) that may help determine eligibility.

g. Vital signs (blood pressure, heart rate/pulse, respiratory rate and temperature). Post-baseline, record the daily highest and lowest temperature measurements. Additional vitals may be taken as needed.

h. Record at least 2 heart rate/pulse measurements taken during a 30 minute period. Record at least 2 blood pressure measurements, or record highest and lowest measurements if continuously monitored, over a 30 minute period.

i. At screening, obtain results of CXR, CT scan, or other imaging tests (eg, echocardiogram, CT scan, MRI, ultrasound) if performed as part of the subject's regular medical care up to 3 days before screening.

j. If clinically indicated and performed as part of subject's regular medical care.

k. Refer to Section 7.4.1 for list of tests. Recommended to repeat at least every 7 days. If immature neutrophils are available, calculate I/T neutrophil ratio using the formula: I/T ratio=Immature cells/Total (mature+immature).

l. For subjects who have been hospitalized for ≥8 hours, calculate urine output over the last 8 hour period.

m. Study treatment may be temporarily withheld at the discretion of the Investigator. See Section 5.5.2. Optional IV antibiotic coverage for Gram-positive organisms, multi-drug resistant Gram-negative organisms, or IV metronidazole for anaerobes may be added per Investigator discretions. See Section 6.2.1.1, Points 2-4.

n. Blood samples for PK (0.3 mL per sample) will be collected following IV infusion of CAZ-AVI (after at least 3 consecutive doses have been administered), at the following time points: 1) anytime within 15 minutes after stopping CAZ-AVI infusion, 2) anytime between 30 minutes and 90 minutes after stopping CAZ-AVI infusion, and 3) anytime between 300 minutes (5 hours) and 360 minutes (6 hours) after stopping CAZ-AVI infusion. If the dosing interval for any cohort is increased from every 8 hour to every 12 hours, then timing of the third PK sample will be changed to anytime between 540 minutes (9 hours) and 600 minutes (10 hours) after stopping CAZ-AVI infusion. Preference should be given to the first and third collection time if only two PK samples are obtained for any reason. For infants weighing less than 1 kg only the first and third PK blood sample will be collected. PK blood samples are NOT to be drawn if the subject received a blood or blood component transfusion within the past 24 hours. For subjects who are at risk from additional blood loss, collection of PK samples will require assessment by the Investigator.

o. Review and record prior and concomitant medications taken or received within 7 days before the first dose of study therapy, including, but not limited to, all antimicrobials, parenteral nutrition, and blood and blood component transfusions. For subjects who are being breast fed, record all medications taken by the lactating mother for 3 days before first dose of study therapy through Late Follow-Up (LFU).

p. Baseline cultures obtained per standard of care should preferably be obtained before any antibacterials are administered. Cultures should be repeated per standard of care upon knowledge of a positive result until sterilization is confirmed.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

Ceftazidime is a bactericidal third generation cephalosporin antibiotic with activity against clinically important Gram-negative Enterobacteriaceae and *Pseudomonas aeruginosa*. Ceftazidime is approved for the treatment of aerobic Gram-negative bacterial infections in adults and children including neonates (from birth). Many years of experience using ceftazidime have accrued in numerous countries worldwide and its tolerability profile is well characterized. Included among the infections treated by ceftazidime are complicated urinary tract infection (cUTI) caused by *Pseudomonas aeruginosa, Enterobacter species (spp.), Proteus spp., Klebsiella spp., and Escherichia coli (E. coli)*; complicated intra-abdominal infection (cIAI), including peritonitis, caused by *E. coli, Klebsiella* spp., *Staphylococcus aureus* (methicillin-susceptible strains); and lower respiratory tract infections caused by *P. aeruginosa, Klebsiella* spp. *E. coli, Enterobacter* spp., and *S. aureus* (methicillin-susceptible strains). Ceftazidime is also approved for use in a wide range of other infections, including but not limited to complicated skin and soft tissue infections (cSSTI), bone and joint infections, bronchopulmonary infections in cystic fibrosis, and bacteremias (Fortum Summary of Product Characteristics [SmPC] 2016;[4] FORTAZ United States Package Insert [USPI] 2014).[5] Like other β-lactam antibiotics, ceftazidime is susceptible to hydrolysis by β-lactamases thereby rendering it inactive. The high and increasing prevalence of β-lactam resistance has reduced the utility of ceftazidime in many countries.

Avibactam is a novel, non-β-lactam, β-lactamase inhibitor. Beta-lactamase inhibition by avibactam is effected through the formation of a stable covalent carbamoyl linkage to the enzyme complex. Although avibactam itself possesses no intrinsic antibacterial activity, it has been shown to restore in vitro activity of ceftazidime against Class A, Class C and some Class D β-lactamase-producing pathogens including those commonly associated with cIAI, cUTI, and nosocomial pneumonia (NP). Avibactam, when combined with ceftazidime, has also been shown to be active against strains that express a combination of β-lactamase types, as well as strains that are concomitantly resistant to other antibacterial classes such as fluoroquinolones. Unlike currently available β-lactamase inhibitors, avibactam does not induce β-lactamase production (Miossec et al., 2013).[6]

A fixed dose combination of ceftazidime-avibactam (referred to hereafter as CAZ-AVI) was approved for use in adults by the FDA on 25 February 2015 and in children three months of age and older on 14 Mar 2019 for cIAI (in combination with metronidazole) and cUTI, and it is marketed under the tradename AVYCAZ.[1] On 24 June 2016, the European Commission granted European Union marketing authorization for the use of CAZ-AVI in adults under the tradename Zavicefta.[2] CAZ-AVI has received regulatory approval in 51 countries worldwide.

The fixed dose combination ceftazidime-avibactam is currently being evaluated globally for pediatric use in HAP/VAP.

CAZ-AVI is indicated in the US and Europe for the treatment of adults with complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI), and hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP). It is also indicated in Europe for the treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options. CAZ-AVI is indicated in the US for the treatment of children three months of age and older with cIAI (in combination with metronidazole) and for children with cUTI.

1.2. Background

CAZ-AVI is currently being evaluated for use in pediatric patients. PK in pediatric subjects aged 3 months to 18 years was investigated in Study D4280C00014, a Phase 1, multicenter, open-label study. In that study pediatric subjects receiving other systemic antibiotic therapy for suspected or confirmed infection were administered a single IV infusion of CAZ-AVI over 120 minutes. A total of 35 subjects were enrolled in the study and 32 received the full infusion treatment, 8 in each of the 4 age cohorts: 1) aged ≥12 to <18 years; 2) aged ≥6 to <12 years; 3) aged ≥2 to <6 years; and 4) age ≥3 months to <2 years.

A population PK model (CAZ-MS-PED-01) for CAZ-AVI in pediatrics was developed using adult PK data and PK data from pediatric subjects in Study D4280C00014. Based on this model, dose regimens were selected for two recently completed Phase 2 pediatric studies, D4280C00015/C3591004 and D4280C00016/C3591005, to assess the safety, tolerability and descriptive efficacy of CAZ-AVI in children age 3 months to less than 18 years with cIAI and cUTI, respectively.

1.3. Rationale for Conducting This Study

The long-established efficacy and safety of ceftazidime in children including neonates (from birth), the mode of action of avibactam, and the available Phase 2 clinical data for CAZ-AVI in pediatrics provide a strong rationale for extending the evaluation of CAZ-AVI into the infant and neonatal population. CAZ-AVI is expected to provide positive clinical outcomes in those pediatrics patients infected with pathogens resistant to β-lactam antibiotics due to the presence of avibactam sensitive β-lactamases. CAZ-AVI has the potential to address the significant unmet clinical need associated with antibiotic resistance in pediatric patients including infants/neonates.

The current study will extend the evaluation of CAZ-AVI into infants and premature neonates by collecting single and multiple dose pharmacokinetic information, safety, tolerability, and descriptive efficacy in newborns less than 3 months of age down to a gestational age of 26 weeks.

The inclusion and exclusion criteria have been chosen in order to select appropriate pediatric subjects for single dose PK assessment in Part A who are already receiving other IV antibiotics for suspected or confirmed bacterial infection. For the multiple dose PK assessment in Part B the enrollment criteria have been chosen to select appropriate pediatric subjects who have suspected or confirmed bacterial infection with aerobic Gram-negative organisms and sufficient severity to require treatment with IV antibiotics. Subjects with

suspected or confirmed central nervous system (CNS) infection are excluded because adequate penetration of CAZ-AVI into the CNS has not been established. The PK sampling and safety assessments are judged to be sufficient to fulfill the primary and secondary objectives of the study.

1.4. Dose Rationale

Dosing for this study is based on modelling and simulation study CAZ-MS-PED-02 (Study 7) which included data from the adult Phase 1, 2, and 3 studies including studies of cIAI, cUTI, and NP, and three prior pediatric studies: 1) D4280C00014, an open-label, single-dose study in hospitalized pediatric patients from 3 months to <18 years of age receiving systemic antibiotic therapy for suspected or confirmed infection; 2) D4280C00015/C3591004 a Phase 2, single-blind, randomized, multicenter, active-controlled, multiple-dose study of CAZ-AVI when given in combination with metronidazole and compared with meropenem in hospitalized pediatric patients from 3 months to <18 years of age with cIAI; and 3) D4280C00016/C3591005 a Phase 2, single-blind, randomized, multicenter, active-controlled, multiple-dose study of CAZ-AVI compared with cefepime in hospitalized pediatric patients from 3 months to <18 years of age with cUTI.

In all population pharmacokinetic (PK) analyses both ceftazidime (CAZ) and avibactam (AVI) concentration time courses have been well described by a linear 2-compartment PK model with first-order elimination. Simulations based on the final population described above were used to provide dose recommendations for all pediatric patients from pre-term neonates to <18 years of age with normal renal function, mild, moderate, or severe renal impairment. Per dose regimen and age scenario sets of 1,000 pediatric PK parameters were simulated with between-subject variability simulated non-parametrically through resampling of individual random effect estimates from the final CAZ and AVI models. The exposure target was defined as achieving at least 50 percent of time during the dosing interval that CAZ and AVI are simultaneously above the minimum inhibitory concentration (MIC) of 8 mg/mL for CAZ and Critical threshold concentration (C_T) of 1.0 mg/L for AVI, respectively. The Probability of Target Attainment (PTA) was defined as the percentage of simulated patients that simultaneously achieved the exposure targets for both CAZ and AVI. The PK/PD targets for CAZ of MIC 8 mg/L and AVI of C_T 1.0 mg/L are the same joint PK/PD targets used to support approval in adults.

A range of mg/kg doses administered over a 2h infusion were simulated for normal renal function. For simulated infants >28 days to ≤3 months of age, CAZ-AVI doses of 30/7.5 mg/kg every 8 hours (q8h) over a 120 minute infusion were predicted to give joint PTAs ≥96% for cUTI, cIAI, and NP and achieve CAZ and AVI maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC_{0-24}) exposures similar to adult exposures. Compared with the reference population (adults with normal renal function), the CAZ geometric mean C_{max} ranged from 93% to 94% and the AUC_{0-24} ranged from 94% to 99%. The AVI geometric mean C_{max} ranged from 95% to 105% and the AUC_{0-24} ranged from 96% to 103%. For simulated full-term neonates, CAZ-AVI doses of 20/5 mg/kg q8h were predicted to achieve ≥96% PTAs for cUTI, cIAI,

and NP while maintaining CAZ and AVI C_{max} and AUC_{0-24} exposures slightly lower than reference adult exposures. The CAZ geometric mean C_{max} ranged from 72% to 73% and the AUC_{0-24} ranged from 82% to 87% of corresponding adult values. The AVI geometric mean C_{max} ranged from 71% to 78% of adult values and the AUC_{0-24} ranged from 77% to 83%. For simulated pre-term neonates, CAZ-AVI doses of 20/5 mg/kg q8h were predicted to achieve ≥99% PTAs for cUTI, cIAI, and NP while maintaining CAZ and AVI C_{max} exposures similar or slightly lower than adults and AUC_{0-24} exposures slightly higher than adults. The CAZ geometric mean C_{max} ranged from 95% to 97% of values for the reference adult patients while the AUC_{0-24} ranged from 130% to 138% of corresponding adult values. The AVI geometric mean C_{max} ranged from 85% to 92% of reference adult values and the AUC_{0-24} ranged from 104% to 112%.

Based on the simulation study CAZ-MS-PED-02 (Study 7), dosing for this study will be initiated using an 8 hour dosing interval and 120 minute infusion for all cohorts with CAZ-AVI doses of: 30/7.5 mg/kg q8h for infants >28 days to <3 months of age (including pre-term infants with corrected age in this interval) and 20/5 mg/kg q8h for full- and pre-term infants. These doses for the ceftazidime component are within the mg/kg/day range for approved doses of 100-150 mg/kg/day in 3 divided doses for infants >2 months of age and 25-60 mg/kg/day in 2 divided doses for neonates and infants ≤2 months of age in the EU (Fortum SmPC, 2016)[4] and the approved doses of 30-50 mg/kg q8h in infants >1 month of age and 30 mg/kg every 12 hours (q12h) in neonates and infants 0-4 weeks of age in the US (FORTAZ USPI, 2014).[5] If emerging PK data during the study suggest that the alternative dosing interval of 12 hours for term and/or pre-term neonates in Cohort 2 and Cohort 3, respectively, would be more appropriate, this information will be provided to Investigators in a written protocol Clarification Memorandum from the Sponsor. Other potential dosing regimens are provided in Appendix 3 which may be utilized only upon written notice from the Sponsor in a protocol Clarification Memorandum. Any dosing modifications provided in a protocol Clarification Memorandum will be incorporated into the next version of the protocol.

1.5. Benefit/Risk and Ethical Assessment

The potential benefit of the study, in general, is the identification of a novel antibiotic combination product that is an effective treatment for infections in infants and neonates, in the face of the changing pattern of antibiotic resistance. In Part A, CAZ-AVI will not be used to treat the infection for which the subject is receiving IV antibiotics, as Part A is not a therapeutic study. The potential benefit to subjects participating in Part B of this study is that they will receive effective antibiotic therapy for their infection. It is possible that CAZ-AVI will not prove to be a sufficiently effective treatment for aerobic Gram-negative organisms in Part B, despite the long established efficacy of ceftazidime alone. This risk is mitigated by the allowed option of adding an aminoglycoside antibiotic, by close monitoring of study subjects, and by management with appropriate other therapies as determined by the Investigator providing treatment.

The risk considerations for this study encompass the known and potential risks for the development product CAZ-AVI and its component products ceftazidime and avibactam. Additionally there may be risks associated with other treatments that may be administered as described in this protocol (ampicillin, vancomycin, or optional aminoglycoside). As the risks for these marketed products are widely available in their respective prescribing information, these risks are not discussed within this section.

The full risk profile for ceftazidime is described in the prescribing information for the product (refer to local ceftazidime product labeling). Important risks as laid out in the warnings and precautions in product labeling for ceftazidime include the following:

- Elevated levels of ceftazidime used in patients with renal impairment have been associated with neurological sequelae such as tremor, myoclonus, seizures, encephalopathy and coma.

The adverse events (AEs) described below for ceftazidime may occur with multiple administrations and are unlikely to occur with the single dose that subjects in Part A will be receiving:

- Antibiotic-associated diarrhea, Clostridium difficile diarrhea, colitis, and pseudomembranous colitis;

- Bacterial overgrowth with nonsusceptible organisms.

The risks for CAZ-AVI in neonates/infants have not been fully elucidated; however, it is assumed that known or potential risks for CAZ-AVI should include those identified in the approved local label for CAZ-AVI, eg the US Package Insert (USPI) (AVYCAZ, 2019)[1] or the EU Summary of Product Characteristics (SmPC) (Zavicefta, 2018).[2] Thus far, no unique risks have been identified for the combination of ceftazidime and avibactam in infants/children. In recently completed study D4280C00015/C3591004, CAZ-AVI plus metronidazole was well tolerated for the treatment of pediatric patients 3 months of age to <18 years of age with cIAI. Highly favorable clinical and microbiological response rates were observed across all patients in the study and against the predominant cIAI pathogens (*E. coli and P. aeruginosa*), and no new safety concerns were identified. In recently completed study D4280C00016/C3591005, CAZ-AVI was generally well tolerated and appeared effective for the treatment of pediatric patients 3 months of age to <18 years of age with cUTI, and no new safety concerns were identified. Side effects identified for the avibactam component of CAZ-AVI include injection site redness and injection site bruising.

Additional information for CAZ-AVI may be found in the single reference safety document (SRSD), which for this study is the CAZ-AVI Investigator Brochure (IB).

2. STUDY OBJECTIVES AND ENDPOINTS

Part A Primary Objective:	**Part A Primary Endpoints:**
To characterize the pharmacokinetics (PK) of a single intravenous dose of CAZ-AVI in hospitalized neonates and infants from birth to <3 months.	CAZ and AVI plasma concentrations by nominal sampling time.
Part A Secondary Objective:	**Part A Secondary Endpoint:**
To evaluate the safety and tolerability of a single intravenous dose of CAZ-AVI in hospitalized neonates and infants from birth to <3 months.	Safety and tolerability endpoints include adverse events (AEs), serious adverse events (SAEs), deaths, discontinuations due to AEs and laboratory abnormalities.

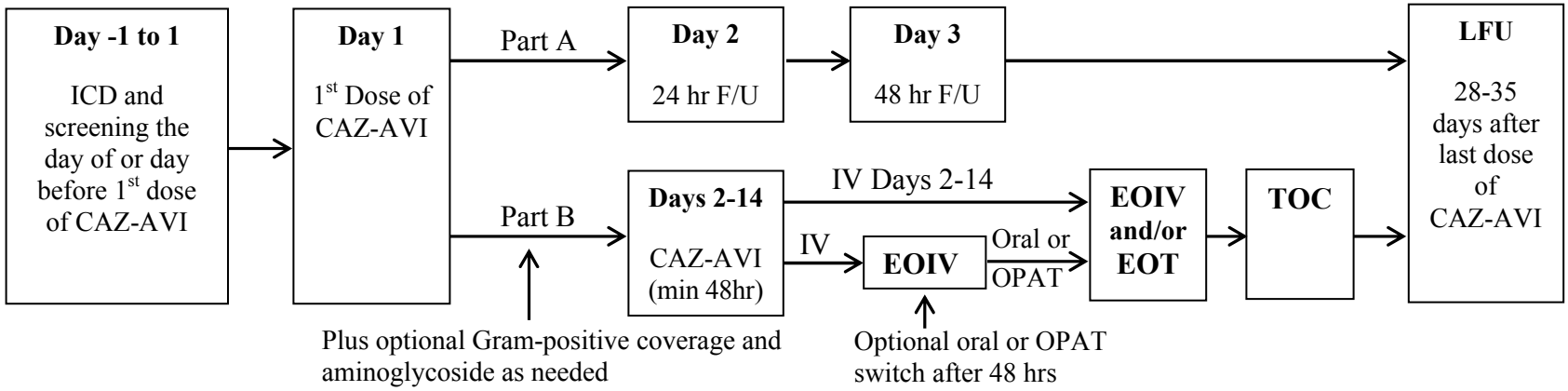
Part B Primary Objective:	**Part B Primary Endpoint:**
To evaluate the safety and tolerability of CAZ-AVI for the treatment of aerobic Gram-negative infection in neonates and infants from birth to <3 months.	Safety and tolerability endpoints include adverse events (AEs), serious adverse events (SAEs), deaths, discontinuations due to AEs and laboratory abnormalities.
Part B Secondary Objectives:	**Part B Secondary Endpoints:**
To evaluate the pharmacokinetic profile of multiple intravenous doses of CAZ-AVI in hospitalized neonates and infants from birth to <3 months.	CAZ and AVI plasma concentrations by nominal sampling time.
To evaluate the efficacy of CAZ-AVI for the treatment of aerobic Gram-negative infection in neonates and infants from birth to <3 months.	Efficacy outcome measures will 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 (micro-Intent-to-Treat analysis set). • Emergent infections.

3. 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.

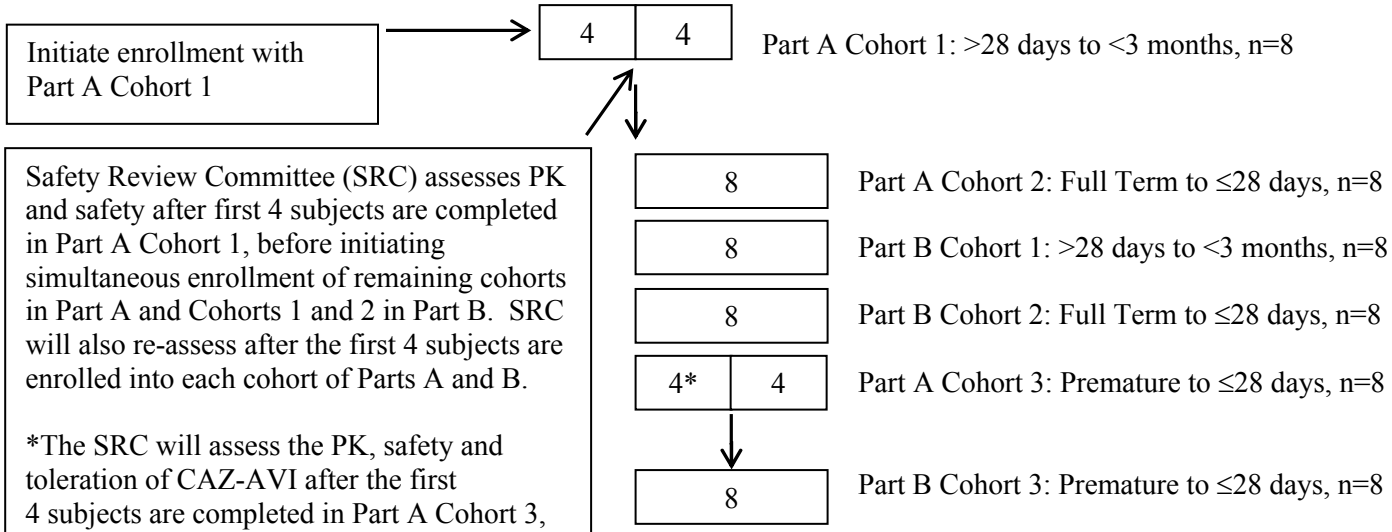
The study outline is provided in Figure 1. The sequence of cohort startup is provided in Figure 2.

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.

Figure 2. Cohort Start Up



4. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

Subject eligibility should be reviewed and documented by an appropriate member of the Investigator's study team before subjects are included in the study.

The target population for single dose Part A is hospitalized neonates and infants with bacterial infection receiving intravenous antibacterial therapy. The target population for multiple dose Part B is hospitalized neonates and infants with suspected or confirmed aerobic Gram-negative bacterial infection requiring intravenous antibacterial therapy, excluding those with suspected or confirmed CNS infection.

The inclusion and exclusion criteria will be assessed by a site Investigator before enrollment of the subject to the study. Clinically indicated antibacterial treatment must not be delayed because a subject is being considered for participation.

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule. If there is uncertainty about whether a specific subject meets inclusion/exclusion criteria this may be discussed with the Medical Monitor, but the Medical Monitor cannot waive any of the enrollment criteria.

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

4.1.1. Inclusion Criteria for All Subjects

1. Evidence of a personally signed and dated informed consent document indicating that the subject's parent(s), legal guardian, or legally acceptable representative has been informed of all pertinent aspects of the study.

2. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

3. Male or female neonates and infants with age at Screening:

    a. Cohort 1: Full term infants (gestational age ≥37 weeks) with chronological age >28 days to <3 months (<89 days) or pre-term infants with corrected age* >28 days to <3 months (<89 days). A maximum of 3 pre-term corrected age infants may be enrolled in each part (A and B) of Cohort 1. Sites will be notified in writing if this limit is reached.

b. Cohort 2: Full term neonates (gestational age ≥37 weeks) from birth to ≤28 days.

c. Cohort 3: Pre-term neonates (gestational age ≥26 to <37 weeks) from birth to ≤28 days.

Gestational age is 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 (Engle, 2004).[3] Corrected age (in weeks) = chronological age in weeks – (40 – gestational age in weeks). See Appendix 2 for calculation of corrected age in days and alternative perinatal age terminologies.

4.1.2. Inclusion Criteria for Part A Subjects Only

1. Hospitalized and receiving intravenous antibacterial therapy for the treatment of a suspected or confirmed bacterial infection.

4.1.3. Inclusion Criteria for Part B Subjects Only

1. Hospitalized with suspected or confirmed aerobic Gram-negative bacterial infection requiring intravenous antibacterial therapy.

2. Subjects must meet at least 1 clinical and 1 laboratory criterion or meet at least 2 of the clinical criteria:

   Clinical Criteria:

   a. Hypothermia (<36°C) OR fever (>38.5°C);

   b. Bradycardia OR tachycardia OR rhythm instability;

   c. Urine output 0.5 to 1 mL/kg/h OR hypotension OR mottled skin OR impaired peripheral perfusion;

   d. Petechial rash OR sclerema neonatorum;

   e. New onset or worsening of apnea episodes OR tachypnea episodes OR increased oxygen requirements OR requirement for ventilation support;

   f. Feeding intolerance OR poor suckling OR abdominal distension;

   g. Irritability;

   h. Lethargy;

   i. Hypotonia.

Laboratory Criteria:

a. White blood cell count $\leq 4.0 \times 10^9$/L OR $\geq 20.0 \times 10^9$/L;

b. Immature to total neutrophil ratio >0.2;

c. Platelet count $\leq 100 \times 10^9$/L;

d. C-reactive protein (CRP) >15 mg/L OR procalcitonin ≥2 ng/mL;

e. Hyperglycemia OR Hypoglycemia;

f. Metabolic acidosis.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

4.2.1. Exclusion Criteria for All Subjects

1. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the Investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.

2. Participation in another clinical study involving investigational drug(s) within 30 days prior to study entry and/or during this study participation or have previously participated in the current study or in another study of CAZ-AVI (in which an active agent was received).

3. Use of potent inhibitors of organic anion transporters OAT1 and/or OAT3 (eg, probenecid, p-aminohippuric acid (PAH), or teriflunomide) are prohibited. This prohibition of OAT1 and/or OAT3 inhibitors also applies to the mothers of any neonates or infants who are breast feeding during the trial.

4. Other acute or chronic medical or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study.

5. Documented history of any hypersensitivity or allergic reaction to any β-lactam antibiotic.

6. Refractory septic shock within 24 hours before screening that does not resolve after 60 minutes of vasopressor therapy.

7. Moderate or severe renal impairment defined as serum creatinine ≥2 times the upper limit of normal (ULN) for age OR urine output <0.5 mL/kg/h (measured over at least 8 hours) OR requirement for dialysis. Deterioration of renal function after enrollment during Part B of the study will be handled on a case-by-case basis in discussion with the Medical Monitor (see Section 5.5.2).

8. Evidence of progressively fatal underlying disease, or life expectancy of ≤60 days.

9. Documented history of seizure.

10. Active acute viral hepatitis or acute hepatic failure.

11. Known *Clostridium difficile* associated diarrhea.

12. Requiring or currently taking antiretroviral therapy for human immunodeficiency virus (HIV) or known HIV positive mother.

13. Any condition (eg, cystic fibrosis, urea cycle disorders), antepartum/peripartum factors, or procedures that would, in the opinion of the Investigator, make the subject unsuitable for the study, place a subject at risk, or compromise the quality of data.

14. Treatment with ceftazidime within 12 hours of CAZ-AVI administration.

4.2.2. Exclusion Criteria for Part A Subjects Only

1. Subject received a blood or a blood component transfusion within 24 hours of the start of CAZ-AVI infusion.

2. Subject is expected to be discharged less than 24 hours after the start of CAZ-AVI infusion.

4.2.3. Exclusion Criteria for Part B Subjects Only

1. At study entry, subject has confirmed or strongly suspected infection with a pathogen known to be resistant to CAZ-AVI or only a Gram-positive pathogen or viral, fungal, or parasitic pathogens as the sole cause of infection.

2. Confirmed or suspected central nervous system (CNS) infection (eg, meningitis, brain abscess, subdural abscess).

3. Anticipated need for antibacterial therapy longer than 14 days (eg, osteomyelitis, endocarditis). This applies to both study treatment with CAZ-AVI as well as adjunctive IV antibacterial treatment for suspected co-infection with Gram-positive organisms or multi-drug resistant Gram-negative organisms.

4. Receipt of more than 24 hours of nonstudy systemic antibacterial treatment for Gram-negative organisms after culture and before administration of study doses of CAZ-AVI. Empiric coverage with an aminoglycoside for suspected multidrug resistant organisms is permitted, provided CAZ-AVI is initiated within 24 hours after culture.

5. Intravenous treatment with chloramphenicol within 24 hours of administration of study doses of CAZ-AVI.

6. Subject is expected to be discharged less than 48 hours after the start of CAZ-AVI infusion.

4.3. Randomization Criteria

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.

4.4. Cohort Enrollment Sequence

Enrollment for this study will begin with Cohort 1 of Part A. 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 delegates will assess the PK, safety and toleration of CAZ-AVI in the first 4 subjects in Cohort 1 of Part A prior to initiating simultaneous enrollment of the remaining cohorts in Part A and Cohorts 1 and 2 in Part B. If CAZ-AVI concentrations or safety/toleration are not as expected in the first 4 subjects in Cohort 1 of Part A, then the SRC in conjunction with the EDMC may recommend a dose adjustment from Appendix 3 and/or a modified enrollment sequence which will be communicated to the study sites in a written protocol Clarification Memorandum and incorporated into the next protocol version. A similar assessment will be conducted after the first 4 subjects are enrolled into each cohort of Part A and Part B. Enrollment will not begin in Cohort 3 of Part B until the SRC has conducted its review of the first 4 subjects in Cohort 3 of Part A. If CAZ-AVI safety, toleration or PK are not consistent with expectations after the first 4 subjects in any Cohort, then it may be necessary to delay or stagger the remaining cohorts to gain more experience, in which case an updated Pfizer and EDMC approved cohort enrollment sequence will be provided to sites in a written protocol Clarification Memorandum.

4.5. Procedures for Handling Incorrectly Enrolled Subjects

Where a subject does not meet all the eligibility criteria, but is enrolled in error and incorrectly started on study treatment, the Investigator should inform the Medical Monitor immediately, and a discussion should occur between the Medical Monitor and the Investigator regarding whether to continue or discontinue the subject from treatment. The Medical Monitor must ensure all decisions are appropriately documented.

4.6. Sponsor’s Qualified Medical Personnel

The contact information for the Sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation at each site.

To facilitate access to appropriately qualified medical personnel on study related medical questions or problems, the subject's parent(s), legal guardian, or legally acceptable representative is provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study numbers, contact information for the Investigator site, and contact details for a contact center in the event that the Investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by Investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the Investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the Investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject's parent(s), legal guardian, or legally acceptable representative directly, and if a parent, legal guardian, or legally acceptable representative calls that number, he or she will be directed back to the Investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational product is Zavicefta (ceftazidime-avibactam [CAZ-AVI]).

5.1. Allocation to Treatment

This is an unblinded, single treatment arm study. All subjects will receive CAZ-AVI.

5.2. Breaking the Blind

This is an open-label study. Blinding procedures are not applicable. The Investigator's knowledge of the treatment should not influence the decision to enroll a particular subject or affect the order in which subjects are enrolled.

5.3. Subject Compliance

Qualified study center personnel will administer the IV study treatment and assure treatment compliance. At a minimum the dose, date, and exact start and stop time of administration of the IV study treatment will be recorded in the appropriate sections of the Case Report Form (CRF) and checked by the monitor at monitoring visits. Deviations from study treatment will be reported and documented.

Subject compliance with dosing administration in Part B will be verified by accounting doses administered. The subject dosing compliance should be within the range of 80% and 120% of expected doses during the time the subject is receiving IV CAZ-AVI. Subject noncompliance cases should be discussed with medical monitors.

5.4. Investigational Product Supplies

All sites will be provided with an Investigational Product (IP) Manual containing detailed instructions on the receipt, storage, dispensing, preparation, and administration of the investigational product, as outlined below. If there is any conflict between this protocol and the IP Manual regarding the handling of the investigational product, the IP Manual will take precedence.

5.4.1. Dosage Form(s) and Packaging

The investigational product, Zavicefta (ceftazidime 2 g/avibactam 0.5 g), will be supplied by Pfizer as a white to yellow powder for concentrate for solution for infusion in a 20 mL glass vial. Each vial contains a fixed dose combination of ceftazidime pentahydrate equivalent to 2 g ceftazidime and avibactam sodium equivalent to 0.5 g avibactam.

Table 1. Identity of Investigational Product

Investigational product	Dosage form and strength
Zavicefta (ceftazidime/avibactam)	2 g/0.5 g powder for concentrate for solution for infusion

5.4.2. Preparation and Dispensing

Detailed instructions for the preparation of CAZ-AVI powder for concentrate for solution for infusion will be provided in the separate IP Manual. The investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. The preparation and administration of all sterile products must be performed using aseptic technique.

Ceftazidime/avibactam powder for concentrate for solution for infusion vials should be reconstituted with 10 mL of sterile water for injection. After reconstitution, 1 mL of solution contains 167.3 mg of ceftazidime and 41.8 mg of avibactam. The reconstituted solution is pale yellow and free of particles. Each vial is for single use only and should be used immediately after reconstitution. The reconstituted solution in the vial should be diluted with a compatible diluent for administration in an IV bag or IV syringe at the appropriate concentration for intravenous infusion.

Any unused product or waste material should be disposed of in accordance with local requirements.

5.5. Administration (Dose and Treatment Regimen)

The prepared doses of CAZ-AVI are intended for intravenous infusion based on age and weight as detailed in Table 2. The dose should generally be calculated based on the subject's first weight of the day on the starting day, although other options such as the birth weight, the "dosing weight" or "drug calculation weight" may be used if that is the local standard practice for weight-based neonatal drug dosing. In all situations the weight used for the dose calculation must be recorded in the CRF as well as the daily weight on the day dosing is started and the daily weight on the day of PK assessment. Administration should be via either an appropriately sized sterile syringe and calibrated syringe pump or IV infusion bag and calibrated IV pump over 120 minutes.

Table 2. CAZ-AVI Weight-based Doses for Each Cohort

Cohort	Age	CAZ-AVI weight-based dose	Infusion		
			Volume	Duration	Frequency
1	>28d* to <3m old	30 mg/kg CAZ 7.5 mg/kg AVI	Varies, will not exceed 2 mL/kg/dose	120 min	q8 hr **(Part B Only)**
2	GA ≥37wk and ≤28d old	20 mg/kg CAZ 5.0 mg/kg AVI			
3	GA ≥26wk to <37wk and ≤28d old	20 mg/kg CAZ 5.0 mg/kg AVI			

GA = Gestational Age; d = days; hr = hours; m = month; min = minutes; wk = week.

*Includes term infants (GA ≥37 weeks) >28 days of age and pre-term infants with corrected age >28 days. Corrected age = Subtract the number of weeks born before 40 weeks of gestation from the chronological age (Engle, 2004).[3]

Potential alternative dosing regimens are listed in Appendix 3, which are to be utilized only upon written confirmation from the Sponsor that a dosing regimen change is necessary for a given cohort or cohorts. The pharmacokinetics of CAZ-AVI will be evaluated after the first 4 subjects are enrolled in each age cohort and as necessary the dosing may be adjusted for the remaining subjects (see Section 4.4).

5.5.1. Part A

On Day 1 subjects in Part A will receive a single IV infusion of CAZ-AVI over a 2-hour (±10 min) period according to their cohort as indicated in Table 2. The infusion can be administered any time during the subject's course of treatment with the other intravenous antibiotic, with the exception that no doses of ceftazidime are permitted within 12 hours of CAZ-AVI infusion. The CAZ-AVI infusion should be timed so as to not interfere with dosing of the other antibiotic.

5.5.2. Part B

On Day 1 subjects in Part B will begin receiving IV CAZ-AVI over a 2-hour (±10 min) period every 8 hours (±1 hour) according to their cohort as indicated in Table 2. The CAZ-AVI dose in Part B should not be adjusted based on fluctuations in daily weight, and it should remain the same throughout the dosing period up to 14 days, unless local standard practice is to reassess all neonatal dosing on a regular basis, such as weekly, and make dose

adjustments for weight changes. In the latter case, CAZ-AVI dosing may be adjusted for weight changes, provided PK assessments are not obtained until at least 3 consecutive doses are administered after any dose change. If a subject's urine output decreases to <0.5 mL/kg/h (measured over at least 8 hours) or serum creatinine level increases ≥2 × ULN during the treatment period, the Medical Monitor should be contacted to discuss the subject's safe continuation in the study. The Investigator should use his or her discretion in determining whether a short period of continued observation or discontinuation of therapy is warranted. Additionally, in instances of rapidly changing renal function, the Investigator should increase the frequency of renal monitoring, depending on the subject's clinical status, extent of renal function change and the Investigator's clinical evaluation. Study treatment may be temporarily withheld at the discretion of the Investigator. Subjects withdrawing from study therapy can be administered alternative therapies at the Investigator's choice, which should be recorded in the CRF. If possible, subjects should still be followed for safety.

5.6. Investigational Product Storage

The Investigator or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

See the IP manual for storage conditions of the product once reconstituted and/or diluted.

Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

5.7. Investigational Product Accountability

The Investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

5.7.1. Destruction of Investigational Product Supplies

The Sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the Investigator site, the Investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.8. Oral Switch Therapy

Subjects in Part B may be switched to oral therapy after at least 48 hours of IV CAZ-AVI if the subject has a good or sufficient clinical response and is tolerating oral fluids or food. The decision to switch to oral therapy is entirely at the Investigator's discretion. If subjects are switched to oral therapy, the End of IV Treatment (EOIV) visit will be conducted at the time the intravenous CAZ-AVI study drug is discontinued. If the subject is discharged from the hospital any remaining study visits may be conducted on an outpatient basis. The choice of oral switch therapy, among the options listed below, should be in line with the approved and marketed drugs in the respective country, and should observe the local specific regulations and local therapeutic guidelines (if existent), regarding posology. For the optional oral switch therapy, the following options are preferred:

1. Oral amoxicillin/clavulanic acid (only in countries where its use for infants/neonates is permitted; according to local guidelines, administered at a dose and formulation per standard of care), or

2. Oral ciprofloxacin (only in countries where its use for infants/neonates is permitted; according to local guidelines, administered at a dose and formulation per standard of care) plus metronidazole (administered at a dose and formulation per standard of care), or

3. Pathogen-based therapy (in discussion with the Medical Monitor). The choice of oral antibacterial agent for pathogen-based therapy will be driven by the results of a susceptibility test, which will be provided to the Investigator by the local laboratory. Initiation of pathogen-based therapy is at the Investigator's discretion. Before administering pathogen-based therapy, the Investigator will discuss the results of the susceptibility test and the selected antibacterial drug (which should be approved for use in infants/neonates) with the Medical Monitor.

The optional oral switch therapies will be sourced locally by the study centers or sourced as agreed between the study centers and Sponsor.

Consult the Summary of Product Characteristics or product package insert, label, and local dosing guidelines for further information regarding dosage, administration, storage, maximum doses, contraindications, warnings, precautions, and adverse effects of oral switch therapies.

5.9. Intravenous Switch Therapy

In rare situations it may be appropriate to discharge subjects in Part B to continue outpatient parenteral antimicrobial therapy (OPAT) at home. The decision to switch to OPAT is entirely at the Investigator's discretion, but subjects cannot continue to receive the CAZ-AVI study drug outside the hospital. If subjects are candidates for OPAT after at least 48 hours of IV CAZ-AVI, Investigators will select the appropriate intravenous antibiotic(s) based on culture results, local therapeutic guidelines, and approved and marketed drugs in their respective countries. If subjects are switched to OPAT, the End of IV Treatment (EOIV) visit will be conducted at the time the intravenous CAZ-AVI study drug is discontinued. After subjects on OPAT are discharged from the hospital any remaining study visits may be conducted on an outpatient basis.

The OPAT therapies will be sourced locally by the study centers or sourced as agreed between the study centers and Sponsor. Consult the Summary of Product Characteristics or product package insert, label, and local dosing guidelines for further information regarding dosage, administration, storage, maximum doses, contraindications, warnings, precautions, and adverse effects of OPAT therapies.

5.10. Concomitant Treatment(s)

Use of potent inhibitors of organic anion transporters OAT1 and/or OAT3 (eg, probenecid, p-aminohippuric acid (PAH), or teriflunomide) are prohibited during the study because they have the potential to alter (decrease) the clearance of avibactam when coadministered. This prohibition on the use of OAT1 and/or OAT3 inhibitors also applies to the mothers of any neonates or infants who are breast feeding during the trial.

Intravenous treatment with chloramphenicol during the study is prohibited within 24 hours of administration of study doses of CAZ-AVI in Part B. Chloramphenicol is antagonistic in vitro with ceftazidime and other cephalosporins, though the clinical relevance of this finding is not known.

Concomitant treatment with ceftazidime is not permitted any time during the study or within 12 hours of CAZ-AVI administration.

In Part A, the use of any other antibiotics is permitted, including other antibiotics combined with beta lactamase inhibitors. In Part B, the use of antibiotics combined with other beta lactamase inhibitors is prohibited, including combinations with the beta lactamase inhibitors sulbactam, tazobactam, clavulanate, and any new beta lactamase inhibitors which become available during the course of the study.

Adjunctive IV antibacterial treatment for suspected co-infection with Gram-positive organisms may be given per standard of care, with preference for ampicillin or vancomycin. If Gram-positive coverage is added empirically and subsequent culture results do not isolate a Gram-positive pathogen, the Investigator should consider discontinuing the additional Gram-positive coverage. Metronidazole may be added to CAZ-AVI to provide coverage for anaerobic organisms. Adjunctive coverage for aerobic Gram-negative organisms is discouraged, but if additional coverage against multi-drug resistant Gram-negative organisms is empirically indicated to ensure adequate therapy while awaiting baseline culture and susceptibility results, additional Gram-negative coverage with aminoglycosides gentamicin or amikacin may be added per standard of care.

Consult the Summary of Product Characteristics, product package insert, label, and local dosing guidelines for information regarding dosage, administration, storage, maximum doses, contraindications, warnings, precautions, and adverse effects for adjunctive antibacterial treatment.

6. STUDY PROCEDURES

Study periods are defined in Figure 1. Details of the study plan and procedures are provided in the SCHEDULE OF ACTIVITIES and are described in detail by visit in the following sections.

6.1. Screening and Enrollment

Prior to any study specific procedures, the subject's parent or parents (depending on local requirements) or legally acceptable representative must provide written informed consent. During the screening period, subjects will be assessed regarding eligibility criteria. Subjects who do not meet all of these criteria must not be enrolled in the study.

6.1.1. Visit 1: Eligibility/Screening Procedures (Day -1 to 1)

Each subject will undergo Screening assessment procedures on the day of or one day prior to the first dose of CAZ-AVI as outlined in the SCHEDULE OF ACTIVITIES. Screening assessments can serve as baseline if they are completed on the same calendar day as Day 1, prior to CAZ-AVI infusion, but they must be completed no earlier than the day before the start of CAZ-AVI infusion, except for laboratory assessments in Part A which may be up to 2 days before the start of CAZ-AVI infusion. If additional assessments are conducted per standard of care prior to the first infusion of CAZ-AVI the assessments closest to the infusion will be considered baseline. Potential subjects who do not meet enrollment criteria may, as appropriate, repeat screening evaluations at a later time for possible enrollment into the study.

6.1.1.1. Clinical Assessments

1. Obtain informed consent.

2. Review the inclusion and exclusion criteria.

3. Obtain a complete medical history, including, but not limited to, history of delivery, antepartum and peripartum antibacterials, vaccinations, congenital abnormalities, surgeries, and all conditions diagnosed after birth.

4. Record demography.

5. Identify, assess, and record any new or ongoing Adverse Events (AEs) or Serious Adverse Events (SAEs).

6. Review and record prior and concomitant medications taken or received within 7 days before the first dose of study therapy, including, but not limited to, all antimicrobials, parenteral nutrition, and blood and blood component transfusions. For subjects who are being breast fed, record all medications taken by the lactating mother during the 3 days before the first dose of study therapy.

7. Perform brief physical examination, including, but not limited to:

    a. Physical findings related to bacterial infection or sepsis;

    b. Presence of central venous catheter (eg, umbilical catheter);

    c. Presence of other medical devices such as ventilator, cardiac devices, cerebrospinal fluid (CSF) shunts, orthopedic transplants, or urinary catheter.

8. Record weight and length.

9. Record vital signs (heart rate/pulse, blood pressure, respiratory rate, temperature) and oxygen saturation:

    a. Record at least 2 heart rate/pulse measurements taken during a 30 minute period.

    b. Record at least 2 blood pressure measurements, or record highest and lowest measurements if continuously monitored, over a 30 minute period.

10. Record imaging study results (eg, chest x-ray, echocardiogram, computerized tomography scan (CT scan), magnetic resonance imaging (MRI), ultrasound) if performed as part of the subject's regular medical care up to 3 days before screening.

6.1.1.2. Laboratory Assessments

1. Obtain blood samples for complete blood count (CBC) with differential and chemistry panel (see Laboratory Manual). For Part A, if the subject is improving and laboratory assessments were performed within 2 days of CAZ-AVI infusion, those test results may be used for eligibility and they do not need to be repeated for screening.

2. If clinically indicated and if blood gases are available (Part B Only), calculate base excess (BE) using the formula:

   $BE = 0.02786 * pCO_2 * 10^{(pH - 6.1)} + 13.77 * pH - 124.58$

   pCO_2 = partial pressure of carbon dioxide (mm Hg).

   pH = negative logarithm of the hydrogen ion concentration (a measure of acidity or alkalinity).

3. If clinically indicated, record CRP and serum procalcitonin levels if tests are performed as part of the subject's regular medical care (Part B Only).

4. Perform urinalysis (see Laboratory Manual).

5. For subjects who have been hospitalized for ≥8 hours, calculate urine output over the last 8 hour period.

6.1.1.3. Microbiological Assessments (Part B Only)

1. If clinically indicated and performed as part of subject's regular medical care, obtain blood culture for testing per Section 7.3.1; cultures should be repeated per standard of care upon knowledge of a positive result until sterilization is confirmed.

2. If clinically indicated, obtain urine culture for testing per Section 7.3.2; cultures should be repeated per standard of care upon knowledge of a positive result until sterilization is confirmed.

3. If clinically indicated and performed as part of subject's regular medical care, obtain other specimens/tissue samples per Section 7.3.3; cultures should be repeated per standard of care upon knowledge of a positive result.

4. Obtain any prior microbiological and clinical data (eg, notes in medical records confirming worsening of signs and symptoms of infection) that may help determine eligibility.

Enroll the subject after verifying that the subject meets all inclusion and no exclusion criteria. There should be no medically inappropriate delay in administration of study therapy.

6.2. Study Period

6.2.1. Visit 2, Study Day 1

Study Day 1 is the day of the first administration of study therapy.

6.2.1.1. Study Therapy Administration

1. Infusion of CAZ-AVI IV over a 2-hour (±10 min) period, according to the cohort as indicated in Table 2. The dose should be calculated based on the subject's first weight of the day on the starting day unless the local standard practice for neonatal weight-based dosing is to use an alternative weight, such as the birth weight (see Section 5.5). For subjects in Part A this will be the only infusion of CAZ-AVI. Subjects in Part B will continue CAZ-AVI infusions every 8 hours. The CAZ-AVI dose in Part B should not be adjusted based on fluctuations in daily weight, and it should remain the same throughout the dosing period up to 14 days, unless local standard practice is to reassess all neonatal dosing on a regular basis, such as weekly, and make dose adjustments for weight changes. In the latter case, CAZ-AVI dosing may be adjusted for weight changes, provided PK assessments are not obtained until at least 3 consecutive doses are administered after any dose change.

2. Part B Only: Optional antibacterial coverage for Gram-positive organisms, dosage per institutional guidelines and Investigator's judgement. IV ampicillin or vancomycin are preferred, but choice of therapy is at the Investigator's discretion.

3. Part B Only: Optional IV aminoglycoside, gentamicin or amikacin, if additional coverage against multi-drug resistant (MDR) Gram-negative organisms is empirically indicated to ensure adequate therapy while awaiting baseline culture and susceptibility results. Choice of aminoglycoside and dosage are per institutional guidelines and Investigator's judgement.

4. Part B Only: Optional IV metronidazole for anaerobes: dosage per institutional guidelines and Investigator's judgement.

6.2.1.2. Clinical Assessments

1. Identify, assess, and record any new or ongoing AEs or SAEs.

2. Record concomitant medications including, but not limited to, all antimicrobials, parenteral nutrition, and blood and blood component transfusions. For subjects who are being breast fed, record all medications taken by the lactating mother.

3. Prior to the start of the infusion, record the findings of a brief physical examination, including, but not limited to, physical findings of infection or sepsis, presence of central venous catheter or other medical devices (if applicable).

4. Record the subject's first weight of the day.

5. Prior to the start of the infusion, record vital signs (heart rate/pulse, blood pressure, respiratory rate, temperature) and oxygen saturation (if available); record the daily highest and lowest temperature measurements.

6. Record adjunctive therapeutic procedures (eg, drainage of foci of infection), if performed.

7. If clinically indicated, obtain results of chest x-ray (CXR), CT scan, or other imaging tests performed as part of the subject's regular medical care.

6.2.1.3. Laboratory Assessments

1. If clinically indicated, prior to the start of the infusion, obtain blood samples for CBC with differential and chemistry panel (see Laboratory Manual).

2. Part B Only: If clinically indicated and if blood gases are available, calculate base excess (BE) using the formula:

   $BE = 0.02786 * pCO2 * 10^{(pH - 6.1)} + 13.77 * pH - 124.58$

3. Part B Only: If clinically indicated, obtain CRP and serum procalcitonin levels.

4. If clinically indicated, prior to the start of the infusion, perform urinalysis (see Laboratory Manual).

5. Calculate urine output over the last 8 hour period.

6.2.1.4. Microbiological Assessments (Part B Only)

1. If clinically indicated and performed as part of subject's regular medical care, obtain blood culture for testing per Section 7.3.1; cultures should be repeated per standard of care upon knowledge of a positive result until sterilization is confirmed.

2. If clinically indicated, obtain urine culture for testing per Section 7.3.2; cultures should be repeated per standard of care upon knowledge of a positive result until sterilization is confirmed.

3. If clinically indicated and performed as part of subject's regular medical care, obtain other specimens/tissue samples per Section 7.3.3; cultures should be repeated per standard of care upon knowledge of a positive result.

6.2.1.5. PK Procedures – Part A Only

Following the infusion of CAZ-AVI, blood samples for PK (0.3 mL per sample) will be collected at the following time points: 1) anytime within 15 minutes after stopping CAZ-AVI infusion, 2) anytime between 30 minutes and 90 minutes after stopping CAZ-AVI infusion, and 3) anytime between 300 minutes (5 hours) and 360 minutes (6 hours) after stopping CAZ-AVI infusion. If the dosing interval for any cohort is increased from every 8 hours to every 12 hours, then timing of the third PK sample will be changed to anytime between

540 minutes (9 hours) and 600 minutes (10 hours) after stopping CAZ-AVI infusion. Preference should be given to the first and last collection time if only two PK samples are obtained. For infants weighing less than 1 kg only the first and third PK blood sample will be collected. PK blood samples are NOT to be drawn if the subject received a blood or blood component transfusion within the past 24 hours. For subjects who are at risk from additional blood loss, collection of PK samples will require assessment by the Investigator.

6.2.2. Visit 3, Study Day 2: Part A Only

6.2.2.1. Clinical Assessments

1. Identify, assess, and record any new or ongoing AEs or SAEs.

2. Record concomitant medications including, but not limited to, all antimicrobials, parenteral nutrition, and blood and blood component transfusions. For subjects who are being breast fed, record all medications taken by the lactating mother.

3. Record the findings of a brief physical examination, including, but not limited to, physical findings of infection or sepsis, presence of central venous catheter or other medical devices (if applicable).

4. Record the subject's first weight of the day.

5. Record vital signs (heart rate/pulse, blood pressure, respiratory rate, temperature) and oxygen saturation; record the daily highest and lowest temperature measurements.

6. Record adjunctive therapeutic procedures (eg, drainage of foci of infection), if performed.

7. If clinically indicated, obtain results of CXR, CT scan, or other imaging tests performed as part of the subject's regular medical care.

6.2.2.2. Laboratory Assessments

1. Obtain blood samples for complete blood count (CBC) with differential and chemistry panel (see Laboratory Manual).

2. Perform urinalysis (see Laboratory Manual).

3. Calculate urine output over the last 8 hour period.

6.2.3. Visit 4, Study Day 3: Part A Only

6.2.3.1. Clinical Assessments

1. Identify, assess, and record any new or ongoing AEs or SAEs.

2. Record concomitant medications including, but not limited to, all antimicrobials, parenteral nutrition, and blood and blood component transfusions. For subjects who are being breast fed, record all medications taken by the lactating mother.

3. Record the findings of a brief physical examination, including, but not limited to, physical findings of infection or sepsis, presence of central venous catheter or other medical devices (if applicable).

4. Record the subject's first weight of the day.

5. Record vital signs (heart rate/pulse, blood pressure, respiratory rate, temperature) and oxygen saturation; record the daily highest and lowest temperature measurements.

6. Record adjunctive therapeutic procedures (eg, drainage of foci of infection), if performed.

7. If clinically indicated, obtain results of CXR, CT scan, or other imaging tests performed as part of the subject's regular medical care.

6.2.3.2. Laboratory Assessments

1. If clinically indicated, obtain blood samples for complete blood count (CBC) with differential and chemistry panel (see Laboratory Manual).

2. If clinically indicated, perform urinalysis (see Laboratory Manual).

6.2.4. Visits 3-15, Study Days 2-14: Part B Only

6.2.4.1. Study Therapy Administration

1. Infusion of CAZ-AVI IV over a 2-hour (±10 min) period q8h, according to the cohort as indicated in Table 2. The CAZ-AVI dose in Part B should not be adjusted based on fluctuations in daily weight, and it should remain the same throughout the dosing period up to 14 days, unless local standard practice is to reassess all neonatal dosing on a regular basis, such as weekly, and make dose adjustments for weight changes. In the latter case, CAZ-AVI dosing may be adjusted for weight changes, provided PK assessments are not obtained until at least 3 consecutive doses are administered after any dose change.

2. Antibacterial coverage for Gram-positive organisms, an aminoglycoside for additional MDR Gram-negative coverage, or metronidazole for anaerobes is considered optional beginning on Day 1 through the entire study at a dosage per institutional guidelines and Investigator's judgement. These optional IV antibacterials may be started and stopped at any time during the study at the discretion of the Investigator.

6.2.4.2. Clinical Assessments

1. Identify, assess, and record any new or ongoing AEs or SAEs.

2. Record concomitant medications including, but not limited to, all antimicrobials, parenteral nutrition, and blood and blood component transfusions. For subjects who are being breast fed, record all medications taken by the lactating mother.

3. Record the findings of a brief physical examination, including, but not limited to, physical findings of infection or sepsis, presence of central venous catheter or other medical devices (if applicable).

4. Record the subject's first weight of the day.

5. Record vital signs (heart rate/pulse, blood pressure, respiratory rate, temperature) and oxygen saturation; record the daily highest and lowest temperature measurements.

6. Record adjunctive therapeutic procedures (eg, drainage of foci of infection), if performed.

7. If clinically indicated, obtain results of CXR, CT scan, or other imaging tests performed as part of the subject's regular medical care.

6.2.4.3. Laboratory Assessments

1. If clinically indicated, obtain blood samples for CBC with differential and chemistry panel (see Laboratory Manual).

2. If clinically indicated and if blood gases are available, calculate base excess (BE) using the formula:

   $BE = 0.02786 * pCO2 * 10^{(pH - 6.1)} + 13.77 * pH - 124.58$

3. If clinically indicated, obtain CRP and serum procalcitonin levels.

4. If clinically indicated, perform urinalysis (see Laboratory Manual).

5. Calculate urine output over the last 8 hour period.

6.2.4.4. Microbiological Assessments

1. If clinically indicated and performed as part of subject's regular medical care, obtain blood culture for testing per Section 7.3.1; cultures should be repeated per standard of care upon knowledge of a positive result until sterilization is confirmed.

2. If clinically indicated, obtain urine culture for testing per Section 7.3.2; cultures should be repeated per standard of care upon knowledge of a positive result until sterilization is confirmed.

3. If clinically indicated and performed as part of subject's regular medical care, obtain other specimens/tissue samples per Section 7.3.3; cultures should be repeated per standard of care upon knowledge of a positive result.

6.2.4.5. PK Procedures

Do not draw PK blood samples if the subject received a blood or blood component transfusion within the past 24 hours. For subjects who are at risk from additional blood loss, collection of PK samples will require assessment by the Investigator.

Obtain 3 single PK blood samples between the end of the third consecutive infusion and before EOIV or Study Day 14 (whichever is earlier). Each sample is 0.3 mL (2 x 0.3 mL for premature infants weighing less than 1 kg). Collection times relative to the start of the infusion are: (1) within 15 minutes after stopping CAZ-AVI infusion, (2) between 30 minutes and 90 minutes after stopping the infusion, and (3) between 300 min (5 hours) and 360 minutes (6 hours) after stopping the infusion. If the dosing interval for any cohort is increased from every 8 hour to every 12 hours, then timing of the third PK sample will be changed to anytime between 540 minutes (9 hours) and 600 minutes (10 hours) after stopping CAZ-AVI infusion. Preference should be given to the first and last collection time if only two PK samples are obtained. For infants weighing less than 1 kg only the first and third PK blood sample will be collected.

6.2.5. End of IV (EOIV): Part B Only

EOIV assessments should be performed within 24 hours after completion of the last infusion of CAZ-AVI or at the time of premature discontinuation of CAZ-AVI or early withdrawal from study (if on IV therapy). The EOIV assessments should be conducted in place of the regular study visit (eg, Days 2 to ≤15) assessments that would have been performed the day of that visit. Study therapy may or may not be given on the same calendar day as EOIV assessments. A subject may be eligible to switch to oral therapy on or after at least 48 hours of IV CAZ-AVI (Section 5.8). EOIV assessments must occur before starting oral switch therapy. If a subject is not switched to oral therapy then the EOIV assessment also serves as the EOT assessment. The following will be performed:

6.2.5.1. Clinical Assessments

1. Identify, assess, and record any new or ongoing AEs or SAEs.

2. Record concomitant medications including, but not limited to, all antimicrobials, parenteral nutrition, and blood and blood component transfusions. For subjects who are being breast fed, record all medications taken by the lactating mother.

3. Record the findings of a brief physical examination, including, but not limited to, physical findings of infection or sepsis, presence of central venous catheter or other medical devices (if applicable).

4. Record the subject's first weight of the day.

5. Record vital signs (heart rate/pulse, blood pressure, respiratory rate, temperature) and oxygen saturation; record the daily highest and lowest temperature measurements.

6. Record adjunctive therapeutic procedures (eg, drainage of foci of infection), if performed.

7. If clinically indicated, obtain results of CXR, CT scan, or other imaging tests performed as part of the subject's regular medical care.

8. Assessment of clinical outcome by the Investigator (Table 5).

6.2.5.2. Laboratory Assessments

1. Obtain blood samples for complete blood count (CBC) with differential and chemistry panel (see Laboratory Manual).

2. If clinically indicated and if blood gases are available, calculate base excess (BE) using the formula:

   $$BE = 0.02786 * pCO2 * 10^{(pH - 6.1)} + 13.77 * pH - 124.58$$

3. If clinically indicated record CRP and serum procalcitonin levels if tests are performed as part of the subject's regular medical care.

4. Perform urinalysis (see Laboratory Manual).

5. Calculate urine output over the last 8 hour period.

6.2.5.3. Oral Switch Therapy Administration

Administer oral switch therapy as appropriate per Investigator discretion.

6.2.5.4. Microbiological Assessments

1. If clinically indicated and performed as part of subject's regular medical care, obtain blood culture for testing per Section 7.3.1; cultures should be repeated per standard of care upon knowledge of a positive result until sterilization is confirmed.

2. If clinically indicated, obtain urine culture for testing per Section 7.3.2; cultures should be repeated per standard of care upon knowledge of a positive result until sterilization is confirmed.

3. If clinically indicated and performed as part of subject's regular medical care, obtain other specimens/tissue samples per Section 7.3.3; cultures should be repeated per standard of care upon knowledge of a positive result.

6.2.6. End of Treatment (Oral or OPAT): Part B Only

The assessments at EOT should be performed within 48 hours after the last dose of oral or OPAT switch therapy or at the time of premature discontinuation of oral or OPAT switch therapy or early withdrawal from study (if on oral or OPAT switch therapy). If a subject does not switch to oral or OPAT therapy, the EOIV assessments for IV CAZ-AVI also serve as the EOT assessments. For subjects receiving oral or OPAT switch therapy only, the

following will be performed. If a subject was previously assessed as a clinical failure, only the safety assessments need to be performed (ie, AEs and SAEs, concomitant medications, adjunctive therapeutic procedures, weight, vital signs, CBC with differential and chemistry panel if clinically indicated and performed as part of subject's regular medical care).

1. Identify, assess, and record any new or ongoing AEs or SAEs.
2. Record concomitant medications including, but not limited to, all antimicrobials, parenteral nutrition, and blood and blood component transfusions. For subjects who are being breast fed, record all medications taken by the lactating mother.
3. Record the findings of a brief physical examination, including, but not limited to, physical findings of infection or sepsis, presence of central venous catheter or other medical devices (if applicable).
4. Record the subject's first weight of the day.
5. Record vital signs (heart rate/pulse, blood pressure, respiratory rate, temperature) and oxygen saturation; record the daily highest and lowest temperature measurements.
6. Record adjunctive therapeutic procedures (eg, drainage of foci of infection), if performed.
7. If clinically indicated, obtain results of CXR, CT scan, or other imaging tests performed as part of the subject's regular medical care.
8. Assessment of clinical outcome by the Investigator (Table 5).

6.2.6.1. Laboratory Assessments

1. If clinically indicated, obtain blood samples for complete blood count (CBC) with differential and chemistry panel (see Laboratory Manual).
2. If clinically indicated and if blood gases are available, calculate base excess (BE) using the formula:

   $$BE = 0.02786 * pCO2 * 10^{(pH - 6.1)} + 13.77 * pH - 124.58$$

3. If clinically indicated, record CRP and serum procalcitonin levels if tests are performed as part of the subject's regular medical care.
4. If clinically indicated, perform urinalysis (see Laboratory Manual).
5. If clinically indicated, calculate urine output over the last 8 hour period.

6.2.6.2. Microbiological Assessments

1. If clinically indicated and performed as part of subject's regular medical care, obtain blood culture for testing per Section 7.3.1; cultures should be repeated per standard of care upon knowledge of a positive result until sterilization is confirmed.

2. If clinically indicated, obtain urine culture for testing per Section 7.3.2; cultures should be repeated per standard of care upon knowledge of a positive result until sterilization is confirmed.

3. If clinically indicated and performed as part of subject's regular medical care, obtain other specimens/tissue samples per Section 7.3.3; cultures should be repeated per standard of care upon knowledge of a positive result.

6.2.7. Test of Cure (TOC): Part B Only

Conduct TOC assessments 7 to 14 days after administration of the last dose of study therapy (IV or oral). If a subject was previously assessed as a clinical failure, only the safety assessments need to be performed (ie, AEs and SAEs, concomitant medications, adjunctive therapeutic procedures, weight, vital signs, CBC with differential and chemistry panel if clinically indicated and performed as part of subject's regular medical care).

6.2.7.1. Clinical Assessments

1. Identify, assess, and record any new or ongoing AEs or SAEs.

2. Record concomitant medications including, but not limited to, all antimicrobials, parenteral nutrition, and blood and blood component transfusions. For subjects who are being breast fed, record all medications taken by the lactating mother.

3. Record the findings of a brief physical examination, including, but not limited to, physical findings of infection or sepsis, presence of central venous catheter or other medical devices (if applicable).

4. Record the subject's first weight of the day.

5. Record vital signs (heart rate/pulse, blood pressure, respiratory rate, temperature) and oxygen saturation; record the daily highest and lowest temperature measurements.

6. Record adjunctive therapeutic procedures (eg, drainage of foci of infection), if performed.

7. If clinically indicated, obtain results of CXR, CT scan, or other imaging tests performed as part of the subject's regular medical care.

8. Assessment of clinical outcome by the Investigator (Table 5).

6.2.7.2. Laboratory Assessments

1. If clinically indicated, obtain blood samples for CBC with differential and chemistry panel (see Laboratory Manual).

2. If clinically indicated, perform urinalysis (see Laboratory Manual).

3. If clinically indicated, calculate urinary output over the last 8 hour period.

6.2.7.3. Microbiological Assessments

1. If clinically indicated and performed as part of subject's regular medical care, obtain blood culture for testing per Section 7.3.1; cultures should be repeated per standard of care upon knowledge of a positive result until sterilization is confirmed.

2. If clinically indicated, obtain urine culture for testing per Section 7.3.2; cultures should be repeated per standard of care upon knowledge of a positive result until sterilization is confirmed.

3. If clinically indicated and performed as part of subject's regular medical care, obtain other specimens/tissue samples per Section 7.3.3; cultures should be repeated per standard of care upon knowledge of a positive result.

6.2.8. Late Follow-Up (LFU)

6.2.8.1. Part A

Follow-up contact will be completed at least 28 calendar days, and up to 35 calendar days after infusion of CAZ-AVI to capture any potential adverse events or serious adverse events. Contact with the subject's parent(s)/legal guardian/legally acceptable representative may be conducted via a telephone call.

6.2.8.2. Part B

Conduct LFU assessments, preferably in person, 28 to 35 days after the last dose of IV CAZ-AVI. The LFU may be conducted via telephone for any subject who has not experienced clinical relapse, did not have ongoing AEs or SAEs at TOC, or did not develop AEs or SAEs since TOC. If symptoms of relapse or new AEs or SAEs are noted, or at the discretion of the Investigator, the subject should be immediately scheduled for an in person visit. If a subject was previously assessed as a clinical failure, only the safety assessments need to be performed (ie, AEs and SAEs, concomitant medications, adjunctive therapeutic procedures, weight, vital signs, CBC with differential and chemistry panel if clinically indicated and performed as part of subject's regular medical care).

1. Identify, assess, and record any new or ongoing AEs or SAEs.

2. Record concomitant medications including, but not limited to, all antimicrobials, parenteral nutrition, and blood and blood component transfusions. For subjects who are being breast fed, record all medications taken by the lactating mother.

3. Record the findings of a brief physical examination, including, but not limited to, physical findings of infection or sepsis, presence of central venous catheter or other medical devices (if applicable).

4. Record weight.

5. Record vital signs (heart rate/pulse, blood pressure, respiratory rate, temperature) and oxygen saturation; record highest and lowest daily temperature measurements.

6. Record adjunctive therapeutic procedures (eg, drainage of foci of infection), if performed.
7. If clinically indicated, obtain blood samples for CBC with differential and chemistry panel (see Laboratory Manual).
8. If clinically indicated, perform urinalysis (see Laboratory Manual).
9. Assessment of clinical outcome by the Investigator (Table 5). The clinical outcome assessed at this visit is for relapse or potential re-infection.

6.3. Subject Withdrawal [Early Termination]

Withdrawal of Consent:

Subjects whose parent(s)/legal guardian/legally acceptable representative request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject's parent(s)/legal guardian/legally acceptable representative specifically withdraws consent for any further contact with the subject, themselves or persons previously authorized to provide this information. Subject's parent(s)/legal guardian/legally acceptable representative should notify the Investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the Investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to Follow-Up:

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject's parent(s)/legal guardian/legally acceptable representative after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject's parent(s)/legal guardian/legally acceptable representative to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the Investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the Investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the Investigator should be reported and documented in the subject's medical records.

Subjects may withdraw from the study at any time at the request of their parent(s)/legal guardian/legally acceptable representative, or they may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events section) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject's parent(s)/legal guardian/legally acceptable representative. All attempts to contact the subject's parent(s)/legal guardian/legally acceptable representative and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The Investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow up with the subject's parent(s)/legal guardian/legally acceptable representative regarding any unresolved adverse events (AEs).

If the subject's parent(s)/legal guardian/legally acceptable representative withdraws the subject from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

Subjects who withdraw from the study may be replaced at the discretion of the Investigator upon consultation with the Sponsor.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the Investigator that may make it unfeasible to perform the test. In these cases the Investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the Investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the Investigator site prior to initiation of the study.

7.1. Pharmacokinetics

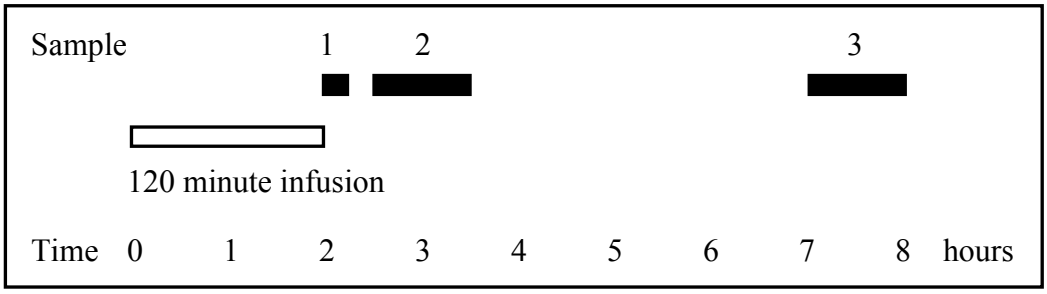
7.1.1. Plasma for Analysis of Ceftazidime - Avibactam

Blood samples (0.3 mL) to provide approximately 0.15 mL of plasma for pharmacokinetic (PK) analysis will be collected into appropriately labeled tubes containing Sodium Fluoride/Potassium Oxalate (custom blue top) at times as shown in Figure 3 and specified in the SCHEDULE OF ACTIVITIES. Venous PK blood samples may be obtained by

venipuncture, through a saline/heparin lock, peripherally inserted central catheter, or through a central line or umbilical vein catheter. Arterial blood sources are not acceptable for PK blood samples. Capillary blood from a heel stick may be utilized if a venous blood sample is not reasonably obtainable. Except for the PK sample to be obtained immediately after the end of the infusion, samples may be drawn from the infusion site only if a multi-lumen catheter is used and these samples must be drawn through a lumen that was not used to deliver drug. PK samples taken immediately after the end of the infusion must not be taken from the infusion site, regardless of whether a multi-lumen catheter is used or not.

Sample collection and handling details are provided in the Laboratory Manual. PK blood samples are NOT to be drawn if the subject received a blood or blood component transfusion within the past 24 hours. For subjects who are at risk from additional blood loss, collection of PK samples will require assessment by the Investigator.

Figure 3. Pharmacokinetic CAZ-AVI Sample Collection Time Points



	All subjects (3 samples/subject)[a]
Sample 1	Within 15 minutes after stopping infusion.
Sample 2	Between 30 minutes and 90 minutes after stopping the infusion.
Sample 3	Between 300 min (5 hours) and 360 minutes (6 hours) after stopping the infusion.[b]
Part A	PK samples will be collected after a single dose of CAZ-AVI has been infused.
Part B	PK samples will be collected after at least 3 consecutive doses of CAZ-AVI have been infused.

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

a. For infants weighing less than 1 kg only the first and third PK blood sample will be collected. If only 2 PK samples are collected for any reason, preference should be given to the first and third collection time.

b. If the dosing interval for any cohort is increased from every 8 hour to every 12 hours in the study, then timing of the third PK sample will be changed to anytime between 540 minutes (9 hours) and 600 minutes (10 hours) after stopping CAZ-AVI infusion.

The date, starting and stop time of infusion and exact time of sample collection must be recorded in the CRF for each sample. By convention, the PK sample collection times in the CRF are specified by the nominal sampling time relative to the infusion start, as shown on the ordinate of Figure 3. The first PK sample collected within 15 minutes of stopping the

infusion has a nominal sampling time of 2 hours, the second PK sample has a nominal sampling time of 2 hours and 30 minutes, and the third sample has a nominal sampling time of 7 hours (or 11 hours if the dosing interval is increased to every 12 hours). If a deviation from the protocol is experienced due to technical difficulties, eg, with the administration of the infusion or PK sampling, the details of the deviation have to be recorded in the CRF.

All efforts will be made to obtain the PK samples within the PK sampling time windows relative to stopping the infusion.

Samples will be analyzed using a validated analytical method in compliance with Pfizer/vendor standard operating procedures (SOPs).

The PK samples must be processed and shipped as indicated in the instructions provided to the Investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the Sponsor. On a case-by-case basis, the Sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

As part of understanding the PK of the investigational product, samples may be used for evaluation of the bioanalytical method, as well as for other internal exploratory purposes. Leftover plasma could be used to assess concentrations of endogenous biomarkers for drug transporters and/or drug metabolizing enzymes. These data will not be included in the CSR.

7.2. Banked Biospecimens

Not applicable.

7.2.1. Additional Research

Not applicable.

7.3. Microbiology

7.3.1. Blood Sample for Culture

If clinically indicated and performed as part of subject's regular medical care, obtain blood for culture at Baseline (preferably before any antibacterials are administered) and at any time through TOC. Cultures should be repeated per standard of care upon knowledge of a positive result until sterilization is confirmed. Perform culture and organism identification at the local or regional laboratory, as applicable. Send all isolates to the central laboratory for organism identification and susceptibility testing.

Refer to the study specific clinical and microbiology laboratory manual for specific procedures pertaining to the collection, processing, storage, and shipment of blood culture or isolates.

7.3.2. Urine Sample for Culture

If clinically indicated per standard of care, obtain urine for culture at Baseline (preferably before any antibacterials are administered) and at any time through TOC. Cultures should be repeated per standard of care upon knowledge of a positive result until sterilization is confirmed. Perform Gram stain, culture, and organism identification at the local or regional laboratory, as applicable. Send all isolates to the central laboratory for organism identification and susceptibility testing.

Refer to the study specific clinical and microbiology laboratory manual for specific procedures pertaining to the collection, processing, storage, and shipment of urine culture or isolates.

7.3.3. Other Specimens and Tissue Samples for Culture

If clinically indicated and performed as part of subject's regular medical care, obtain other specimen and tissue samples from potential foci of infection for culture as clinically indicated at Baseline (preferably before any antibiotics are administered) and at any time through TOC. Cultures should be repeated per standard of care upon knowledge of a positive result. Perform Gram stain (if applicable), culture, and organism identification at the local or regional laboratory. Send all isolates to the central laboratory for organism identification and susceptibility testing.

Refer to the study specific microbiology and clinic laboratory manual for specific procedures pertaining to the collection, processing, storage, and shipment of other specimens/tissues for culture or isolates.

7.4. Safety Assessments

Subjects must be evaluated by a physician or an appropriately trained health care professional at every visit, and the evaluation must be documented. The procedures discussed below will be completed at the designated visits.

7.4.1. Laboratory Safety Assessments

Blood samples and urine samples will be collected at screening baseline and EOIV, if applicable. Samples may also be collected at any time during the treatment period, at TOC and LFU if clinically indicated.

The following laboratory variables will be measured:

Table 3. Laboratory Safety Variables

Chemistry panel	*Hematology panel*	*Urinalysis*
Albumin	Hematocrit	Appearance (color, clarity)
Alkaline phosphatase	Hemoglobin	Bilirubin
Alanine aminotransferase	Red Blood Cell count	Glucose
Aspartate aminotransferase	White Blood Cell count	Ketones
Bilirubin, total and direct	Eosinophils[b]	Leukocyte esterase
Blood urea nitrogen/urea	Lymphocytes[b]	Nitrite
Calcium	Monocytes[b]	pH
Chloride	Neutrophils[b]	Protein
Creatinine	Neutrophils, immature[b]	Specific gravity
Glucose, nonfasting[a]	Platelets	Urobilinogen
Potassium		
Sodium		
Bicarbonate (HCO3)[a]		
Lactate[a]		
pH[a]		
C reactive protein[a]		
Procalcitonin[a]		
Alkaline phosphatase		

a. Test may be used for eligibility, but is not mandatory for eligibility if other eligibility criteria are met.

b. Absolute count and/or %.

7.5. Blood Volume

This protocol complies with European Union's recommendations for blood loss associated with pediatric research (Anonymous, 2017)[7] and the World Health Organization guidelines "Blood Sample Volumes in Child Health Research: Review of Safe Limits" (Howie, 2011).[8] To minimize risk from blood loss associated with this study, standard of care laboratory results will be used whenever possible. All safety laboratory tests will be limited to local processing. In addition, pediatric blood collection tubes will be used and capillary method of blood draw will be implemented whenever feasible. PK samples will be collected from subjects unless deemed unsafe due to the risk from additional blood loss (per the Investigator's judgment).

Table 4 shows the maximum volume of blood that will be drawn from each subject for the purposes of the study, apart from blood that is taken as part of subject's normal standard of care. The volume drawn for study purposes may be lower, as samples taken as standard of care will be used where possible. The combined volume of all blood samples taken from a subject by the end of the study for investigational laboratory tests (ie, CBC with differential, chemistry panel, and PK analyses) is to be no more than 2.4cc/kg or 10cc total whichever is less. Any deviation from this should be clinically justified.

Table 4. Volume of Blood to be Drawn from Each Subject

Assessment/Procedure	Study Visit			Total
Part A	**Screening**	**Day 1**	**Day 2**	
Part B	**Screening**	**Days 2-14**	**EOIV**	
CBC with differential[a]	0.3 mL		0.3 mL	0.60 mL
Chemistry Panel[a]	0.3 mL		0.3 mL	0.60 mL
PK Blood Sample[b]		3 x 0.3 mL		0.90 mL
Total	0.6 mL	0.9 mL	0.6 mL	2.1 mL

Abbreviation: CBC=complete blood count; EOIV=End of IV.

a. Not to be repeated if obtained on the same day per standard of care.

b. Three PK samples (0.3 mL each) to be taken on Day 1 for Part A and during the period from Day 2 to Day 14 for Part B, according to the SCHEDULE OF ACTIVITIES. For premature infants <1 kg only 2 x 0.3 mL PK samples will be collected.

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the Investigator **are to be reported regardless of whether the event is determined by the Investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on

previously forwarded reports. In the rare situation that the Investigator does not become immediately aware of the occurrence of an event, the Investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the Investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the Investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious AE that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the Investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The Investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject's parent(s)/legal guardian/legally acceptable representative. In addition, each study subject's parent(s)/legal guardian/legally acceptable representative will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal [Early Termination] section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject's parent(s)/legal guardian/legally acceptable representative provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including the Late Follow-Up (LFU) Visit (a minimum of 28 calendar days after the last administration of the investigational product).

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the Investigator becomes aware of them; at a minimum, all SAEs that the Investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the Investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator, and Pfizer concurs with that assessment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the Investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator, and Pfizer concurs with that assessment.

8.1.5. Causality Assessment

The Investigator's assessment of causality must be provided for all AEs (serious and non-serious); the Investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An Investigator's causality assessment is the determination of whether there exists a reasonable

possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the Investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor. If the Investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the Investigator determines that an SAE is associated with study procedures, the Investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;

- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the Investigator or Sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);

- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

If required on the AE page of the CRF, the Investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the Investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the Sponsor.

The subject should return to the Investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an

anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the Liver Function Text (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of Investigator awareness.

8.4.3.1. Exposure During Pregnancy

Not applicable.

8.4.3.2. Exposure During Breastfeeding

Not applicable.

8.4.3.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the Investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the Investigator site file.

8.4.4. Medication Errors and Lack of Efficacy

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors and lack of efficacy.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors and lack of efficacy*	All (regardless of whether associated with an AE)	Only if associated with an SAE

*For lack of efficacy (particularly for studies conducted with vaccines, contraceptives, and products used in the treatment of life-threatening diseases or conditions [eg, anti-infectives]), see the Lack of Efficacy section below.

8.4.4.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the Sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the Investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

8.4.4.2. Lack of Efficacy

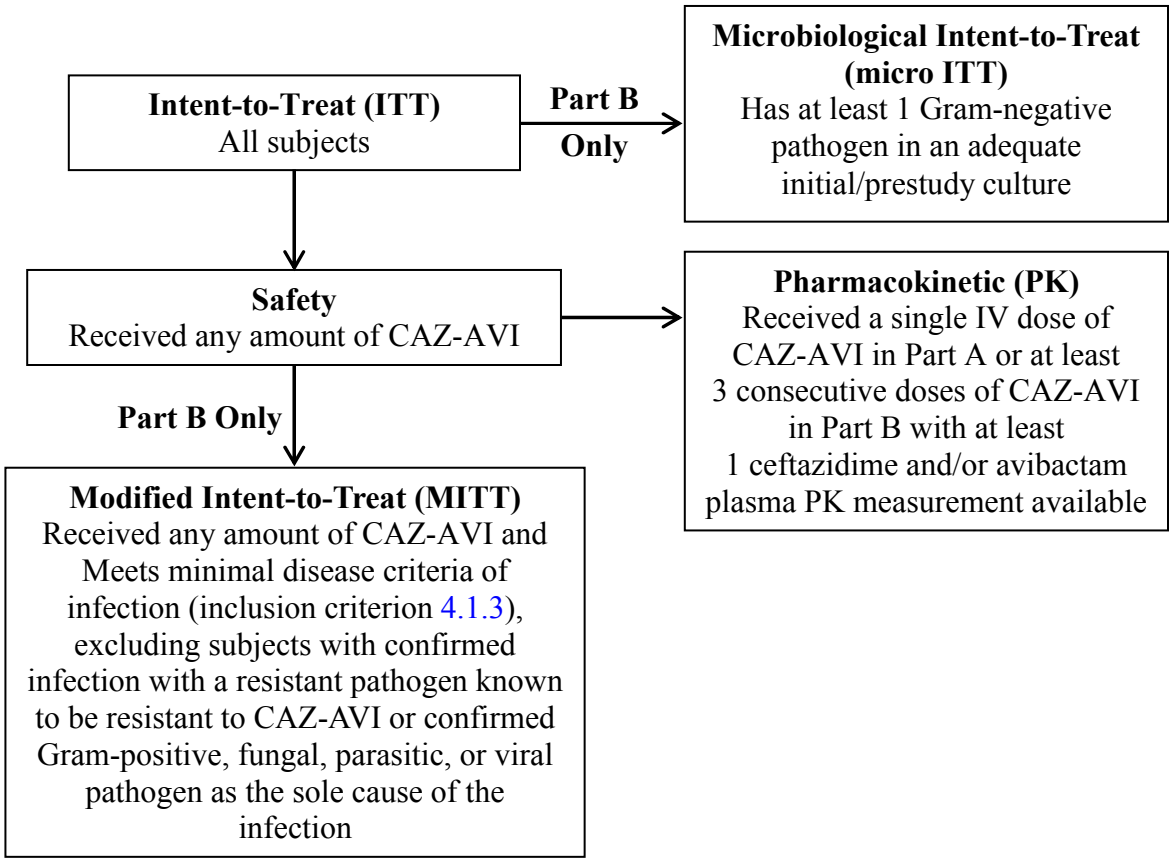
Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the Sponsor and finalized before database lock. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

Analysis sets are described below and in Figure 4.

Figure 4. Study Analysis Sets



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

9.1. Sample Size Determination

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. The sample size (48 subjects; 3 cohorts of 16 subjects) is considered adequate to evaluate the pharmacokinetics of CAZ-AVI in neonates and infants and to provide critical insight into safety and toleration in this

population. Similarly, the sample size in Part B (24 subjects, 3 cohorts of 8 subjects) is considered adequate to provide insight into efficacy in this suspected or confirmed aerobic Gram-negative bacterial infection population. Subjects who are not evaluable for PK (received a single IV dose of CAZ-AVI in Part A or at least 3 consecutive doses of CAZ-AVI in Part B with at least 1 ceftazidime and/or avibactam plasma measurement available) will be replaced.

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

The PK analysis set will consist of all subjects who received a single IV dose of CAZ-AVI in Part A or at least 3 consecutive doses of CAZ-AVI in Part B with at least 1 ceftazidime and/or avibactam plasma PK measurement available. A listing of ceftazidime and avibactam plasma concentrations at the nominal sampling time 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, using the PK analysis set for Cohorts 1 to 3, 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.

9.3. Safety Analysis (Primary Objective Part B, Secondary Objective Part A)

The safety analysis set will consist of all subjects who received any amount of IV study dose of CAZ-AVI. Parts A and B will be summarized separately in addition to an overall safety summary. No inferential statistical tests will be performed for any safety analyses. For each safety parameter, the last assessment made before the first dose of study therapy will be used as the baseline for all analyses. Summaries of demographics and other baseline characteristics will be provided. The incidence of 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. Descriptive statistics of observed results and the change from baseline to selected postbaseline time points will be presented for clinical laboratory results and vital signs. Tabulations and

listings of data for vital signs, weight, 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.

9.4. Efficacy Analysis (Secondary Objective Part B)

The Intent-to-Treat (ITT) analysis set is defined as all subjects who have been enrolled in each part of the study, regardless of whether or not treatment was received.

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

An assessment of clinical outcome will be made by the Investigator at EOIV, EOT, TOC and LFU. Possible outcomes as defined in Table 5 are clinical cure, clinical improvement (oral/OPAT switch subjects only), clinical failure, or indeterminate. A favorable clinical outcome is clinical cure or clinical improvement. An outcome of clinical failure at EOIV will be carried forward to the subsequent visits. Clinical outcomes will be summarized for the ITT, the Modified Intent-To-Treat (MITT) and the micro ITT Analysis Sets from Part B. The MITT Analysis Set will include all subjects who received any amount of CAZ-AVI and who met minimal disease criteria described in the inclusion criteria 4.1.3, defined as the presence of at least 1 clinical criterion and at least 1 laboratory criterion or 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 from the MITT (a list of microorganisms that are considered pathogens will be provided in the SAP). Proportions of subjects with a favorable efficacy response will be displayed overall and within each age cohort. The number and percentage of subjects classified as clinical cure at EOIV, EOT, TOC, and LFU will be tabulated.

Microbiological responses will be summarized (also descriptively) only for the Microbiological ITT (micro ITT) Analysis Set from Part B including all subjects from the Part B ITT Analysis Set who have at least 1 Gram-negative pathogen in an adequate initial/prestudy culture.

9.4.1. Efficacy Response Definitions

Table 5. Definition of Clinical Response Categories at the EOIV, EOT, TOC and LFU

Clinical Response	Definition
Clinical Cure	Resolution of all acute signs and symptoms of infection or improvement to such an extent that no further antibacterial therapy is required.
Clinical Improvement[a]	Subjects who switch to oral therapy and meet all of the following criteria at EOIV: • Afebrile (temperature ≤38.0°C) for at least 24 hours. • Absence of new and improvement in at least 1 symptom or sign (ie, fever, pain, tenderness, elevated WBCs, elevated CRP) from Baseline and worsening of none.
Clinical Failure[b]	Subjects who received ≥48 hours of study treatment and meet any of the following: • Discontinuation of study therapy due to insufficient therapeutic effect, including persistence, incomplete clinical resolution, worsening in signs and symptoms of infection, or isolation of a resistant pathogen that requires alternative nonstudy antibacterial therapy. • Discontinuation of study therapy due to a study therapy related AE and requirement for alternative nonstudy antibacterial therapy for infection. • Death in which infection is contributory.
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: • Death in which infection is clearly noncontributory. • Lost to follow up. • Extenuating circumstances precluding classification as a cure or failure. • Diagnosis of CNS infection, osteomyelitis, endocarditis, or NEC at any time after enrollment. • Received <48 hours of study therapy.

Abbreviations: AE=adverse event; CNS=central nervous system; NEC=necrotizing enterocolitis.

a. Clinical improvement is only applicable at EOIV for subjects who are being switched to oral therapy after less than 14 days of IV CAZ-AVI.

b. A clinical failure at EOIV will be carried forward to EOT, TOC and LFU.

9.4.2. Microbiological Response Definitions

The per-pathogen microbiological outcome categories at TOC are defined in Table 6. Favorable microbiological outcomes are eradication or presumed eradication.

Baseline pathogens 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. Rules for determination of pathogens will be described in the SAP.

Table 6. 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.

Per-subject microbiological response at TOC will be determined programmatically based on individual outcomes for each baseline pathogen, as per Table 7.

Table 7. Per-Subject Microbiological Response

Number of pathogens at baseline	Pathogen 1 Outcome at TOC	Pathogen 2 Outcome 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

Pathogens first appearing after Baseline ("emergent infections") until the LFU are categorized as in Table 8, 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 8. 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.

9.5. Interim Analysis

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 the SAP. 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.

9.6. 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.

9.7. 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.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The Investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the Investigator site may be subject to review by the Institutional Review Board (IRB)/Ethics Committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The Investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the Investigator will cooperate with Pfizer or its agents to prepare the Investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The Investigator site and Investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The Investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the Investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the Investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The Investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the Investigator or by an authorized staff member to attest that the

data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the Investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the Investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer. The Investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another Investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The Investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the Investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the Investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the Investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of subject personal data. Such measures will include omitting subject names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, subject names will be removed and will be replaced by a single, specific numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, subject-specific code. The Investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

The informed consent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The Investigator must ensure that each study subject's parent(s), legal guardian, or legally acceptable representative is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the subject's personal data. The Investigator further must ensure that each study subject, or his or her legally acceptable representative, or parent(s) or legal guardian if a minor, is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The source documents must record how the Investigator determined that the person signing the consent was the subject's legally acceptable representative and the consent signer's relationship to the study subject (eg, parent).

The Investigator, or a person designated by the Investigator, will obtain written informed consent from the subject's parent(s), legal guardian, or legally acceptable representative before any study-specific activity is performed. The Investigator will retain the original of each subject's signed consent document.

12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the Investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the Investigator will inform Pfizer immediately of any urgent safety measures taken by the Investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the Investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of subjects have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination, but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

The end of the trial in all other participating countries is defined as 'the last visit of the last subject undergoing the study' or the date of study closure in the case of early study termination, whichever date is later.

The study may be terminated at individual centers if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. The Sponsor may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with CAZ-AVI.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of CAZ-AVI at any time.

If a study is prematurely terminated, Pfizer will promptly notify the Investigator. After notification, the Investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the Principal Investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The Investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The Investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the Investigator agrees that the first publication is to be a joint publication covering all Investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the Investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

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Appendix 1. Abbreviations

This following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{0-24}	Area under the plasma concentration-time curve from time zero to 24 hours
AVI	Avibactam
BE	Base excess
CAZ	Ceftazidime
CAZ-AVI	Ceftazidime-avibactam
CBC	Complete blood count
CGA	Corrected gestational age
cIAI	Complicated intra-abdominal infection
CK	Creatine kinase
C_{max}	Maximum (or peak) plasma concentration
CNS	Central nervous system
CRF	Case Report Form
CRP	C-reactive protein
CSA	Clinical study agreement
CSF	Cerebrospinal fluid
cSSTI	Complicated skin and soft tissue infections
C_T	Critical threshold concentration (AVI concentration high enough to provide protection to the CAZ component)
CT	Clinical trial
CTA	Clinical trial application
CT scan	Computed tomography scan
cUTI	Complicated urinary tract infection
CXR	Chest x-ray
DILI	Drug-induced liver injury
EC	Ethics committee
E-DMC	External Data Monitoring Committee
EDP	Exposure during pregnancy
eGFR	Estimated glomerular filtration rate
EOT	End of Treatment
EOIV	End of Intravenous
ESBL	Extended-spectrum β-lactamase
EU	European Union
EudraCT	European clinical trials database
GA	Gestational age
GCP	Good clinical practice

Abbreviation	Term
GGT	Gamma-glutamyl transferase
HAP	Hospital-acquired pneumonia
HIV	Human immunodeficiency virus
IB	Investigator Brochure
ICH	International conference on harmonization
IND	Investigational new drug application
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
KPC	Klebsiella pneumoniae carbapenemase
LFT	Liver function test
LFU	Late follow-up
MDR	Multidrug resistant
MedDRA	Medical dictionary for regulatory activities
MIC	Minimum Inhibitory Concentration (lowest drug concentration that prevents visible microorganism growth)
MITT	Modified intent-to-treat
MRI	Magnetic resonance imaging
N/A	Not applicable
NEC	Necrotizing enterocolitis
NP	Nosocomial pneumonia
OAT	Organic anion transporter
OPAT	Outpatient parenteral antimicrobial therapy
PCD	Primary completion date
PCR	Polymerase chain reaction
pCO_2	Carbon dioxide partial pressure
PD	Pharmacodynamic
pH	Negative logarithm of the hydrogen ion concentration (a measure of acidity or alkalinity)
PI	Principal investigator
PK	Pharmacokinetic
PMA	Postmenstrual age
PT	Prothrombin time
PTA	Probability of Target Attainment (probably of achieving the specified drug exposure target)
q12h	Every 12 hours
q8h	Every 8 hours
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SmPC	Summary of Product Characteristics

Abbreviation	Term
SOP	Standard Operating Procedure
SRC	Safety Review Committee
SRSD	Single reference safety document
spp.	Species
TBili	Total bilirubin
TOC	Test of Cure
ULN	Upper limit of normal
US	United States
USPI	United States Package Insert
VAP	Ventilator associated pneumonia

Appendix 2. Calculation of Corrected Age for Pre-Term Infant Eligibility for Cohort 1

Pre-term infants are eligible for Cohort 1 if they have a corrected age >28 days to <3 months (<89 days). The corrected age formula in Section 4.1.1 can be rearranged and expressed in days as follows:

Corrected age (in weeks) = chronological age in weeks – (40 – gestational age in weeks)

Corrected Age (days) = Chronological Age (days) + Gestational Age (days) – 280

Example 1: Infant born at 26 weeks gestation (182 days)
Age since birth 19 weeks (133 days)
Corrected Age (days) = 133 + 182 – 280 = 35 days (eligible)

Example 2: Infant born at 28 weeks 3 days gestation (199 days)
Age since birth 24 weeks 1 day (169 days)
Corrected Age (days) = 169 + 199 – 280 = 88 days (eligible)

Example 3: Infant born at 35 weeks gestation (245 days)
Age since birth 17 week 5 days (124 days)
Corrected Age (days) = 124 + 245 – 280 = 89 days (ineligible)

An alternative terminology frequently used to describe infant age during the perinatal period is Postmenstrual Age (PMA), also known as Corrected Gestational Age (CGA). The PMA or CGA is the gestational age plus the chronological age since birth. PMA or CGA is usually described in number of weeks. A preterm infant born at a gestational age of 33 weeks who is currently 10 weeks old (chronological age) would have a PMA or CGA of 43 weeks.

Eligibility can be determined using PMA or CGA using the following formula.

Corrected Age (days) = PMA or CGA (days) – 280

Example 1: Infant born at 26 weeks gestation (182 days)
Age since birth 19 weeks (133 days)
PMA or CGA (days) = 133 + 182 = 315 days (45 weeks)
Corrected Age (days) = 315 – 280 = 35 days (eligible)

Example 2: Infant born at 28 weeks 3 days gestation (199 days)
Age since birth 24 weeks 1 day (169 days)
PMA or CGA (days) = 169 + 199 = 368 days (52 weeks 4 days)
Corrected Age (days) = 368 – 280 = 88 days (eligible)

Example 3: Infant born at 35 weeks gestation (245 days)
Age since birth 17 week 5 days (124 days)
PMA or CGA (days) = 124 + 245 = 369 days (52 weeks 5 days)
Corrected Age (days) = 369 – 280 = 89 days (ineligible)

Appendix 3. Table of Potential Alternative Doses of CAZ-AVI for Infants and Neonates

No alternative doses from this table are to be used except upon confirmation from the Sponsor in a written protocol Clarification Memorandum including the dosing rationale, any changes to the cohort enrollment sequence, and instructions for preparing and administering the alternative dose. If the dosing interval for any cohort is increased from 8 hours to 12 hours, then timing of the third PK sample will be changed to anytime between 540 minutes (9 hours) and 600 minutes (10 hours) after stopping CAZ-AVI infusion.

Starting dose regimens for this protocol are underlined and bolded.

	Dose (CAZ/AVI)
A	**>28 days to <3 months**
A1	25/6.25 mg/kg q8h
A2	**30/7.5 mg/kg q8h**
A3	35/8.75 mg/kg q8h
B	**birth to ≤28 days (term)**
B1	25/6.25 mg/kg q12h
B2	25/6.25 mg/kg q8h
B3	**20/5 mg/kg q8h**
B4	20/5 mg/kg q12h
B5	15/4.75 mg/kg q8h
C	**birth to ≤28 days (preterm)**
C1	25/6.25 mg/kg q12h
C2	**20/5 mg/kg q8h**
C3	20/5 mg/kg q12h
C4	15/4.75 mg/kg q8h
C5	15/4.75 mg/kg q12h