Official Protocol Title:	A Phase 2/3 Open-label, Randomized, Active-controlled Clinical Study to Evaluate the Safety, Tolerability, Efficacy and Pharmacokinetics of MK-7655A in Pediatric Participants From Birth to Less Than 18 Years of Age With Confirmed or Suspected Gramnegative Bacterial Infection
NCT number:	NCT03969901
Document Date:	20-JUL-2023

TITLE PAGE

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Protocol Title: A Phase 2/3 Open-label, Randomized, Active-controlled Clinical Study to Evaluate the Safety, Tolerability, Efficacy and Pharmacokinetics of MK-7655A in Pediatric Participants From Birth to Less Than 18 Years of Age With Confirmed or Suspected Gram-negative Bacterial Infection

Protocol Number: 021-05

Compound Number: MK-7655A

Sponsor Name: Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

NCT	NCT03969901
EU CT	Not applicable
EudraCT	2019-000338-20
JAPIC-CT	Not applicable
WHO	Not applicable
UTN	Not applicable
IND	108754

Approval Date: 20 July 2023

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 5	20-JUL-2023	The primary reason for this amendment is to clarify the infection types necessary for inclusion of participants aged birth to <3 months in the study.
Amendment 4	30-SEP-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Amendment 3	15-DEC-2021	Amendment 3 (Global) Reasons for the amendment: • To communicate the dosing regimen of MK-7655A for participants enrolled in Age Cohorts 4 and 5, based on the interim review of safety, tolerability, and PK data from PN20 and Age Cohorts 1 through 3 of PN021, and • To add piperacillin/tazobactam IV to the list of comparator medications allowed for participants with cIAI.
Amendment 2	27-AUG-2019	Amendment 2 (Global) Reason for the amendment: To decrease the planned enrollment numbers (including overall, by age group, and by infection site).
Amendment 1	28-JAN-2019	Amendment 1 (Global) Reason for the amendment: To correct the EudraCT Number.
Original Protocol	19-NOV-2018	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 021-05

Overall Rationale for the Amendment:

The primary reason for this amendment is to clarify the infection types necessary for inclusion of participants aged birth to <3 months in the study.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 5.1, Inclusion Criteria	Revised text to clarify the type of infection required for enrollment of participants aged birth to <3 months in the study.	This change was made to address investigator/site feedback. The rationale is further supported by the need to clarify the infection types necessary for inclusion of participants aged birth to <3 months in the study.
Other Changes in Amendment		
Throughout	The structure of the protocol has been updated.	To comply with current industry regulations and guidelines. This restructuring does not affect the clinical or regulatory integrity of the protocol. All other relevant changes and their primary reasons are included for completeness.
Title Page	Added NCT identifying number.	To add regulatory agency identifying number.
Section 1.1, Synopsis - Hypotheses, Objectives, and Endpoints	Revised text explaining there are no hypotheses evaluated in this study.	To clarify that there is no hypothesis testing in this study.

Section Number and Name	Description of Change	Brief Rationale
Section 1.1, Synopsis – Intervention Groups and Duration Table	Revised column headers and abbreviations in Interventions table.	To align with the EU CTR.
Section 1.1, Synopsis - Intervention Groups and Duration Table	Added that IMI/REL is administered as a 60-minute infusion.	To provide additional clarity about route of administration and align with Table 1.
Section 1.1, Synopsis - Intervention Groups and Duration Table	Added note after table referring to Table 2 where the interventions are presented by infection type.	To reference supplementary material.
Section 1.2, Schema	Revised Figure 2 to change the number of participants for Cohort 1 to ≤12 and for Cohorts 2 and 3 to ≥20.	To align with PIP commitment.
Section 1.2, Schema	Revised Figure 2 to change the number of participants for Cohorts 4 and 5 to ≥28.	To align with the minimum enrollment targets for Cohorts 4 and 5.
Section 1.3, Schedule of Activities	Revised text to state (1) that vital signs should be collected daily during IV intervention, (2) that follow-up safety laboratory tests can be taken at either EFU or LFU through 14 days after EOT, and (3) that screening procedures should be completed before randomization.	To further clarify the timing of these procedures.
Section 1.3, Schedule of Activities	Revised text to refer to Table 4 for minimizing blood volumes in neonates.	To clarify the reduced number of blood collection timepoints required in neonates.
Section 1.3, Schedule of Activities	Added text stating that repeat catheterization is not required from participants unable to provide a clean urine specimen for post-baseline culture.	To clarify the requirements for urine specimen collection.

Section Number and Name	Description of Change	Brief Rationale
Section 2.2.2, Preclinical and Clinical Studies	Added PN016 to list of completed clinical studies.	To reflect the current status of the clinical development program.
Section 2.2.3, Ongoing Clinical Studies	Removed PN016.	To reflect the current status of the clinical development program.
Section 3, Hypotheses, Objectives, and Endpoints	Revised text explaining there are no hypotheses evaluated in this study.	To clarify that there is no hypothesis testing in this study.
Section 4.1, Overall Design	Revised the text describing enrollment targets for HABP/VABP and cIAI combined.	To align with enrollment targets for the evaluated infection types.
Section 4.1, Overall Design	Added text to explain that an interim analysis may be performed to assess safety, tolerability, efficacy, and PK when final data from Age Cohorts 1 to 3 are available.	To provide an option for interim analysis of all data from Age Cohorts 1 to 3.
Section 4.2.1.2, Rationale for Exclusion of Patients With Meningitis	Added the various options for meningitis evaluation, including LP or other procedures or assessments.	To clarify the options allowed for ruling out meningitis.
Section 4.4, Beginning and End-of-Study Definition	Added the definition of end of study for the purposes of analysis and reporting and the definition of local start of the study when an EEA Member State is included.	To align with the EU CTR.
Section 4.4, Beginning and End-of-Study Definition	Added a cross-reference to Section 7.3.	To clarify definition of lost to follow-up by referring to Section 7.3.
Section 4.4.1, Clinical Criteria for Early Study Termination	Removed text and instead added a cross-reference to Appendix 1.10.	To ensure clarity regarding when the Sponsor may stop the study or study-site participation.

Section Number and Name	Description of Change	Brief Rationale
Section 5, Study Population	Revised text for specific populations as applicable to the study.	To clarify the collection, use, and confidentiality of demographic data provided by the participants.
Section 5.1, Inclusion Criteria	Change in term from "participant" to "individual" regarding eligibility.	To ensure clarity and intent of this section.
Section 5.2, Exclusion Criteria	Added text to exclusion criterion #4 to further define ileal loop reflux. Revised text in exclusion criterion #8 to add clarity regarding empiric antibiotic usage for suspected meningitis. Revised text in exclusion criterion #9 to include patients <3 months of age without suspected meningitis and to specify that the note pertains to all participants.	To add clarity to exclusion criteria.
Section 6.1, Study Intervention(s) Administered	Revised column headers, dose formulations, abbreviations, and notes in Table 1 - Interventions Table.	To align with the EU CTR.
Section 6.1, Study Intervention(s) Administered	Added footnote to Table 1 explaining where to find generic names for protocol-allowed comparator medications by infection type and referred to Table 2 for additional information listed by infection type.	To clarify the study interventions by infection type.
Section 6.1, Study Intervention(s) Administered	Added Table 2 – Intervention, Dose, and Regimen by Infection Type.	To facilitate understanding of the study interventions.
Section 6.5, Concomitant Therapy	Added text regarding COVID-19 vaccine allowance.	To clarify COVID-19 vaccine information.

Section Number and Name	Description of Change	Brief Rationale
Section 7.1, Discontinuation of Study Intervention	Revised text regarding monitoring of participants who discontinue study intervention and deleted redundant text.	To ensure clarity and intent of the section.
Section 8, Study Assessments and Procedures	Table 4: Merged cells and added footnotes to explain requirements regarding approximate blood volumes drawn at early and late follow-up visits combined.	To clarify blood volumes to be collected from neonates.
Section 8.1.6, Assignment of Screening Number	Added text regarding pretrial screening logs and removal of participant-identifying information.	To allow collection of participant screening logs.
Section 8.1.7, Assignment of Treatment/Randomization Number	Removed the terms “treatment” and “treatment allocation.”	To simplify wording for random treatment assignment.
Section 8.1.8, Study Intervention Administration	Added text to describe who is qualified to administer study intervention(s).	To clarify who may administer study intervention.
Section 8.1.8.1.2, Optional Oral Switch (cIAI, cUTI)	Deleted “q6h” in study intervention description.	To make preceding text relevant to any dosing schedule.
Section 8.1.8.1.2, Optional Oral Switch (cIAI, cUTI)	Added text stating that repeat catheterization not required for post-baseline cultures.	To align with note in SoA pertaining to urine culture collection.
Section 8.3.4, Meningitis Evaluation	Restructured paragraph to list together the various options for meningitis evaluation, including LP or other procedures or assessments.	To clarify the options allowed for ruling out meningitis.

Section Number and Name	Description of Change	Brief Rationale
Section 8.4, Adverse Events, Serious Adverse Events, and Other Reportable Safety Events	Added that investigators need to document if an SAE was associated with a medication error, misuse, or abuse. Clarified that collection is related to SUSARs and the collection of SAEs only.	To align with the EU CTR.
Section 8.4.1, Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information	In Table 10, added text to reporting requirements for pregnancy/lactation exposure and for cancer.	To clarify reporting requirements for pregnancy/lactation and cancer.
Section 8.4.5, Pregnancy and Exposure During Breastfeeding	Added text advising the investigators to report pregnancy complications and medical reasons for elective terminations as AEs or SAEs.	To ensure investigators are reporting medical reasons for elective termination of pregnancy.
Section 8.4.7, Events of Clinical Interest	Clarified definition of a potential DILI.	To improve consistency.
Section 9.1, Statistical Analysis Plan Summary	Revised the text describing enrollment targets for HABP/VABP and cIAI combined.	To align with enrollment targets for the evaluated infection types.
Section 9.6.2, Statistical Methods for Safety Analyses	Clarified definition of a potential DILI.	To improve clarity and consistency.
Section 9.7, Interim Analyses	Added text to explain that an interim analysis may be performed to assess safety, tolerability, efficacy, and PK when final data from Age Cohorts 1 to 3 are available.	To provide an option for interim analysis of all data from Age Cohorts 1 to 3.
Section 9.9, Sample Size and Power Calculations	Revised the text describing enrollment targets for HABP/VABP and cIAI combined.	To align with enrollment targets for the evaluated infection types.

Section Number and Name	Description of Change	Brief Rationale
Appendix 1, Section 10.1.3 - Data Protection	Added statement specifying that Sponsor will conduct this study in compliance with data protection regulations.	To align with updated Code of Conduct 306.1.
Appendix 1, Section 10.1.7 - Compliance with Law, Audit, and Debarment	Added paragraph to provide guidance to investigators in countries with serious breach reporting requirements and to define "serious breach."	To align with the EU CTR.
Appendix 1, Section 10.1.10 - Study and Site Closure	Added text to sentence regarding premature closure of a study site.	To add clarity regarding who can notify the site's IRB/IEC and how.
Appendix 3, Section 10.3.1 Definitions of Medication Error, Misuse, and Abuse	Added definitions of medication error, misuse, and abuse.	To align with the EU CTR.
Appendix 3, Section 10.3.2 - Definition of AE	Added "medical device" and "combination product" to the definition of study intervention.	To add clarity to AE definitions.
Appendix 3, Section 10.3.2 - Definition of AE	Replaced "Sponsor's product" with "study intervention" to be consistent with rest of protocol.	To improve consistency throughout the document.
Appendix 3, Section 10.3.5 - Recording AE and SAE	Replaced "Sponsor's product" with "study intervention" to be consistent with rest of protocol.	To improve consistency throughout the document.
Appendix 5, Section 10.5.1 - Definitions	Expanded the definition of WOCBP.	To provide consistency and clarity related to contraceptive language within this section.
Appendix 5, Section 10.5.2 - Contraceptive Requirements	Revised text for contraceptives allowed during the study.	To align with CTFG 1.1 Recommendations related to contraception.

Section Number and Name	Description of Change	Brief Rationale
Appendix 8, Section 10.8.3 - cUTI	Added sentence specifying the collection of a urine specimen from which pyuria is identified should be obtained within 48 hours prior to randomization.	To align with investigator feedback that pyuria is intermittent in neonates.
Appendix 9, Section 10.9.3 - cUTI	Added meropenem IV to the list of drugs allowed for the treatment of cUTI.	To align with local standard of care.
Appendix 10, Abbreviations	Moved List of Abbreviations to end of appendices and updated numbering of Appendices.	To align with other protocols and make abbreviations easier to find.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2/3 Open-label, Randomized, Active-controlled Clinical Study to Evaluate the Safety, Tolerability, Efficacy and Pharmacokinetics of MK-7655A in Pediatric Participants From Birth to Less Than 18 Years of Age With Confirmed or Suspected Gram-negative Bacterial Infection

Short Title: Open-label Active-control Pediatric Safety, Efficacy, PK Study of MK-7655A

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

There are no formal statistical hypotheses to be evaluated in this study.

The following objectives and endpoints will be evaluated in pediatric participants from birth to less than 18 years of age with confirmed or suspected gram-negative bacterial infection involving 1 of 3 primary infection types: HABP/VABP, cIAI, or cUTI:

Primary Objective	**Primary Endpoint**
To evaluate the safety and tolerability of IMI/REL (imipenem/cilastatin/relebactam) from the first dose of intravenous (IV) study intervention through 14 days after the end of therapy (EOT)	Adverse events (AEs) IV study intervention discontinuations due to AEs
Secondary Objectives	**Secondary Endpoints**
To evaluate the efficacy of IMI/REL by assessing all-cause mortality at Day 28 postrandomization and clinical and microbiological response at the EOT, Early Follow-up (EFU, 7 to 14 days after EOT), and Late Follow-up (LFU, 7 to 14 days after EFU) visits	All-cause mortality Favorable clinical response Favorable microbiological response
To characterize the PK profile of imipenem and relebactam following administration of IMI/REL	Plasma concentrations of imipenem and relebactam $AUC_{0\text{-}24hr}$ and C_{eoi} for imipenem and relebactam %T>MIC for imipenem

Overall Design:

Study Phase	Phase 2/3
Primary Purpose	Treatment
Indication	Bacterial infection in pediatric populations
Population	Participants from birth to less than 18 years of age with confirmed or suspected gram-negative bacterial infection
Study Type	Interventional
Intervention Model	Parallel This is a multisite study.
Type of Control	Active Control Without Placebo
Study Blinding	Unblinded open-label
Blinding Roles	No blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 4 years from the time the first participant (or their legally acceptable representative) provides documented informed consent/assent until the last participant's last study-related contact.

Number of Participants:

Approximately 140 participants will be randomized in a 3:1 ratio to receive IMI/REL or active control as described in Section 9.9.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
IMI/ REL	IMI/REL	relebactam, imipenem, cilastatin 250/500/500 mg	Age Cohort 1: 500/250 mg q6h Age Cohort 2: 15/7.5 mg/kg q6h Age Cohort 3: 15/7.5 mg/kg q6h Age Cohort 4: 15/7.5 mg/kg q**6**h Age Cohort 5: 15/7.5 mg/kg q**8**h All administered as 60-minute infusions	IV Infusion	cIAI and cUTI: Total duration of all study intervention: Minimum 5 days (IV alone or IV then oral, of which at least 3 days must be IV alone before optional oral switch) up to a maximum of 14 days; HABP/VABP: Minimum 7 days up to a maximum of 14 days.	Test Product
Active Control	Acceptable control options for each infection type	Per authorized PI, SPC, or international treatment guidelines	Per authorized PI, SPC, or international treatment guidelines	IV Infusion	cIAI and cUTI: Total duration of all study intervention: Minimum 5 days (IV alone or IV then oral, of which at least 3 days must be IV alone before optional oral switch) up to a maximum of 14 days; HABP/ VABP: Minimum 7 days up to a maximum of 14 days. All administered per authorized PI, SPC, or international treatment guidelines.	Comparator

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
IMI/ REL	Acceptable oral switch options for cIAI and cUTI	Per authorized PI, SPC, or international treatment guidelines	Per authorized PI, SPC, or international treatment guidelines	Oral	Per authorized PI, SPC, or international treatment guidelines	Systemically Prescribed
Active Control	Acceptable oral switch options for cIAI and cUTI	Per authorized PI, SPC, or international treatment guidelines	Per authorized PI, SPC, or international treatment guidelines	Oral	Per authorized PI, SPC, or international treatment guidelines	Systemically Prescribed

cIAI=complicated intra-abdominal infection; cUTI=complicated urinary tract infection; EDC=electronic data collection; HABP/VABP=hospital-acquired or ventilator-associated bacterial pneumonia; IMI/REL=imipenem/cilastatin/relebactam (MK-7655A); IV=intravenous; PI=Package Insert; PO=per os (by mouth); q6h=every 6 hours; q8h=every 8 hours; SPC=Summary of Product Characteristics.

Note: In both intervention arms (IMI/REL and Active Control), participants with cIAI or cUTI may have an optional switch to a specified oral antibacterial therapy after the indicated minimum number of days of IV study intervention at the investigator's discretion based on the participant's clinical condition and local standard of care. The choice of oral switch therapy should be guided by culture results and based on local antibiotic susceptibility patterns.

Note: Protocol-allowed comparator medications for each infection type are detailed by generic drug name in the EDC system, EDC guidelines, and Appendix 9.

Note: Study intervention, dose, and regimen are listed by infection type in Table 2.

IMI/REL Dose by Age Cohort

Age Cohort	Age Range	IMI/REL Dose[a]
1	12 to <18 years	500/250 mg q6h
2	6 to <12 years	15/7.5 mg/kg q6h
3	2 to <6 years	15/7.5 mg/kg q6h
4	3 months to <2 years	15/7.5 mg/kg q**6**h[b]
5	Birth to <3 months	15/7.5 mg/kg q**8**h[b]

FDC=fixed-dose combination; IMI/REL=imipenem/cilastatin/relebactam (MK-7655A); q6h=every 6 hours; q8h=every 8 hours.

[a] Doses for all age cohorts will be administered as 60-minute infusions and will not exceed the adult maximum single dose of IMI/REL 500 mg/250 mg. IMI/REL is provided as a single-vial FDC; therefore, the dose for each component will be adjusted proportionally during preparation.

[b] Initial doses of IMI/REL for participants in Age Cohorts 4 and 5 were selected based on results from the single-dose safety and pharmacokinetics (PK) study in pediatric participants from birth to less than 18 years of age with proven or suspected gram-negative infections (MK-7655A-020) and confirmed based on review of safety, tolerability, efficacy, and PK data from Age Cohorts 1 through 3 in the current study (PN021). Initial doses for Age Cohorts 4 and 5 have been communicated to investigators and sites via Protocol Amendment (03) prior to initiation of enrollment of Age Cohorts 4 and 5.

Total Number of Intervention Groups/Arms	2 treatment arms (IMI/REL or Active Control)
Duration of Participation	Each participant will participate in the study for approximately 44 days from the time that the participant (or their legally acceptable representative) provides documented informed consent/assent through the final contact. After a screening phase of up to 2 days, each participant will receive all assigned study intervention for a total of a minimum of 5 days (cIAI, cUTI, IV alone or IV then oral, of which at least 3 days must be IV alone before optional oral switch) or 7 days (HABP/VABP, IV alone) up to a maximum of 14 days of all study intervention (IV alone or IV then oral). After the end of all study intervention, each participant will be followed for up to 28 days.

Study Governance Committees:

Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No

Study governance considerations are outlined in Appendix 1.

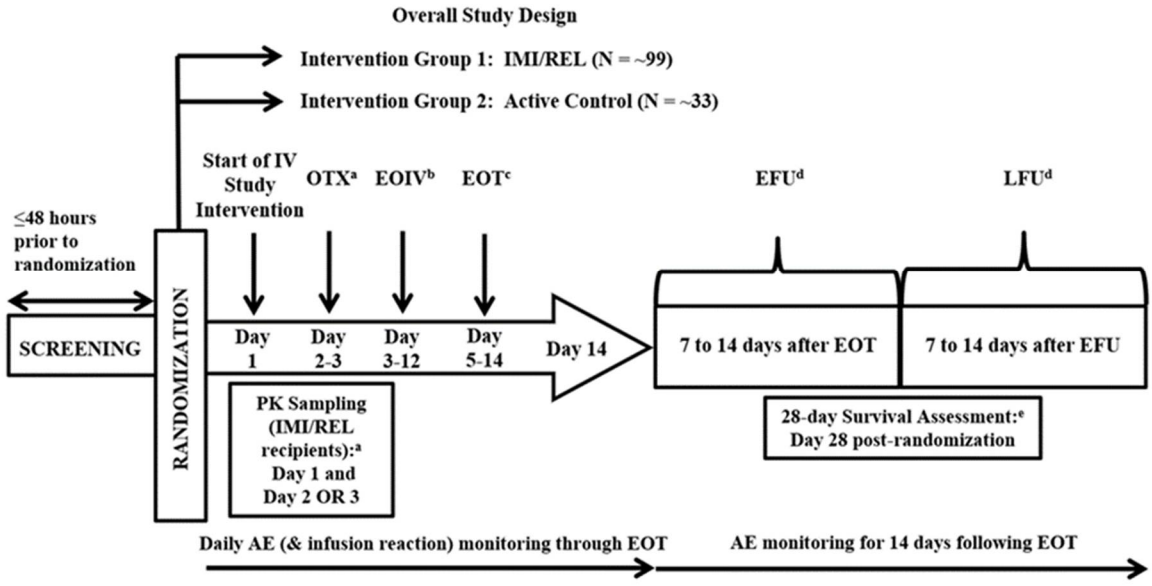
Study Accepts Healthy Participants: No

A list of abbreviations used in this document can be found in Appendix 10.

1.2 Schema

The study design is depicted in Figure 1 and the enrollment plan is depicted in Figure 2.

Figure 1 Study Design Diagram



AE=adverse event; cIAI=complicated intra-abdominal infection; cUTI=complicated urinary tract infection; EFU=early follow-up; EOIV=end of IV therapy; EOT=end of therapy; HABP/VABP=hospital-acquired or ventilator-associated bacterial pneumonia; IMI/REL=fixed-dose combination imipenem/cilastatin and relebactam (MK-7655A); IV=intravenous; LFU=late follow-up; OTX=on therapy; PK=pharmacokinetic.

[a] Participants receiving IMI/REL will have blood samples for PK analysis collected on Day 1 at 3 time points: (1) 30 minutes prior to the start of the first dose of IV study intervention; (2) within 10 minutes after the end of the first infusion; and (3) at 2 to 6 hours after the start of the first infusion; and once at the OTX visit (on Day 2 OR Day 3) at 2 to 6 hours after the start of any infusion that day.

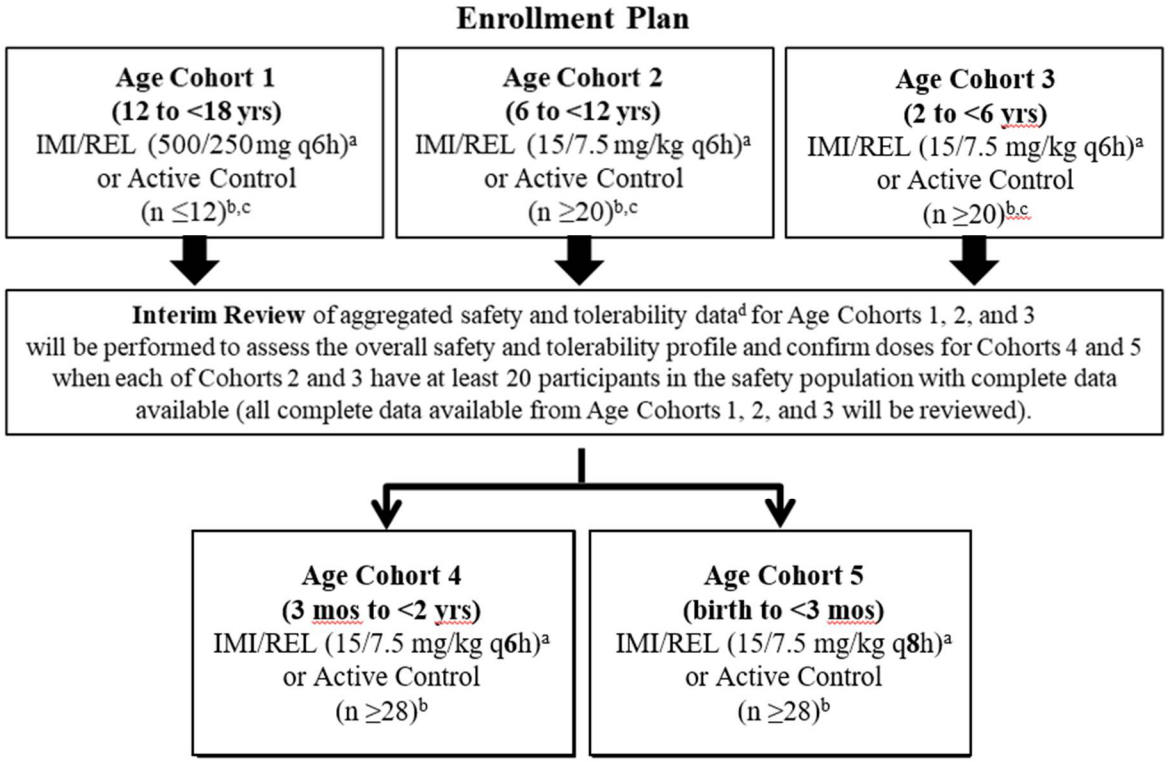
[b] The EOIV visit will occur only in participants with cIAI or cUTI whom the investigator deems eligible to switch to oral antibacterial therapy (after completion of at least 3 days of IV alone) based on the participant's clinical condition and local standard of care. If performed, the EOIV visit must occur ≤24 hours after the last IV dose.

[c] The total duration of all study intervention (IMI/REL or active control) must be a minimum of 5 days (cIAI and cUTI, IV alone or IV then oral, of which at least 3 days must be IV alone before optional oral switch) or 7 days (HABP/VABP, IV alone) up to 14 days (IV alone or IV then oral). Participants with bacteremia or Pseudomonas aeruginosa infection should receive 14 days of antibiotic therapy. Extension beyond 14 days requires Sponsor approval. Participants with cIAI or cUTI who are switched to oral therapy will have the EOT visit ≤24 hours after the last oral dose. For all participants, EOT is the end of all study intervention, and the EOT visit must occur ≤24 hours after completion of the last IV or oral dose.

[d] Safety and efficacy assessments must occur at the EOIV (for participants who switch to oral therapy), EOT, EFU, and LFU visits.

[e] The 28-day survival assessment is to be performed on Day 28 post-randomization at either the EFU or LFU visit or by telephone call on Day 28 (+3 days) post-randomization.

Figure 2 Enrollment Plan



eDMC=external data monitoring committee; IMI/REL=imipenem/cilastatin/relebactam (MK-7655A); IV=intravenous; mos=months; PK=pharmacokinetic; q6h=every 6 hours; q8h=every 8 hours; yrs=years.

[a] Dose for any age cohort will not exceed the maximum adult single IV dose of IMI/REL 500 mg/250 mg. IMI/REL will be administered as a 60-minute IV infusion for all cohorts.

[b] Target enrollment is approximately 140 participants to target having 132 participants in the safety population (ie, who received at least 1 dose of study intervention).

[c] No more than 84 participants will be enrolled across Age Cohorts 1, 2, and 3.

[d] PK and/or efficacy data will be provided to the eDMC upon request to support benefit-to-risk evaluation.

1.3 Schedule of Activities

Study Period	**Screening**	**Intervention**				**Follow-up: up to 42 days post-randomization**			**DC**	**Notes**
Visit Number/Title	**1 Screening[a]**	**2 Day 1[b]**	**3 OTX[b]**	**4 EOIV[c] (oral switch only)**	**5 EOT[d] (all)**	**6 EFU[e]**	**7 LFU[e]**	**TC[f]**	**U[g]**	
Scheduled Day	**Day -2 to 1**	**Day 1**	**Day 2-3**	**Day 3-14**	**Day 5-14**	**7-14 days after EOT**	**7-14 days after EFU**	**28 days post-randomization**	**DC**	
Scheduling Window	**≤48 hr pre-randomization**	**NA**	**NA**	**≤24 hr post-final IV dose**	**≤24 hr post-final dose**	**NA**	**NA**	**+3 days**	**NA**	
Administrative Procedures										
Informed Consent/Assent	X									Documented informed consent from the participant's legally acceptable representative and age-appropriate assent.
Inclusion/ Exclusion Criteria	X									
Participant Identification Card	X	X								Treatment/ randomization number added at time of randomization.
Medical History, including full assessment of details of infection-site diagnoses	X									

Study Period	**Screening**	**Intervention**				**Follow-up: up to 42 days post-randomization**			**DC**	**Notes**
Visit Number/Title	**1 Screening[a]**	**2 Day 1[b]**	**3 OTX[b]**	**4 EOIV[c] (oral switch only)**	**5 EOT[d] (all)**	**6 EFU[e]**	**7 LFU[e]**	**TC[f]**	**U[g]**	
Scheduled Day	**Day -2 to 1**	**Day 1**	**Day 2-3**	**Day 3-14**	**Day 5-14**	**7-14 days after EOT**	**7-14 days after EFU**	**28 days post-randomization**	**DC**	
Scheduling Window	**≤48 hr pre-randomization**	**NA**	**NA**	**≤24 hr post-final IV dose**	**≤24 hr post-final dose**	**NA**	**NA**	**+3 days**	**NA**	
Prior/Concomitant Medication Review	X	X	X	X	X	X	X		X	For breastfed participants, include mother's medications.
Intervention Randomization and Stratification		X								
IRT Contact		X	←-------- If applicable -------→						X	Required for any local or central laboratory abnormalities in serum creatinine or weight changes that may result in a CrCl value meeting discontinuation criteria and for additional IMI/REL supply.
IMI/REL or Active Control Administration[c]		←---------- Daily ---------- →								Table 1and Table 3
Safety Procedures										
Full Physical Examination	X									

Study Period	**Screening**	**Intervention**				**Follow-up: up to 42 days post-randomization**			**DC**	**Notes**
Visit Number/Title	**1 Screening[a]**	**2 Day 1[b]**	**3 OTX[b]**	**4 EOIV[c] (oral switch only)**	**5 EOT[d] (all)**	**6 EFU[e]**	**7 LFU[e]**	**TC[f]**	**U[g]**	
Scheduled Day	**Day -2 to 1**	**Day 1**	**Day 2-3**	**Day 3-14**	**Day 5-14**	**7-14 days after EOT**	**7-14 days after EFU**	**28 days post-randomization**	**DC**	
Scheduling Window	**≤48 hr pre-randomization**	**NA**	**NA**	**≤24 hr post-final IV dose**	**≤24 hr post-final dose**	**NA**	**NA**	**+3 days**	**NA**	
Directed Physical Examination		X	X	X	X	X	X		X	
Height	X									
Weight	X	←---------- If applicable ---------→								See IRT Contact Note and Section 8.3.2.
Vital Signs (heart rate, blood pressure, respiratory rate, temperature)	X	← Daily during IV study intervention →				X	X		X	On Day 1, assess prior to the initiation of IV study intervention. Perform assessments daily during IV study intervention, and at the EOIV (as applicable) and EOT visits.

Study Period	**Screening**	**Intervention**				**Follow-up: up to 42 days post-randomization**			**DC**	**Notes**
Visit Number/Title	**1 Screening[a]**	**2 Day 1[b]**	**3 OTX[b]**	**4 EOIV[c] (oral switch only)**	**5 EOT[d] (all)**	**6 EFU[e]**	**7 LFU[e]**	**TC[f]**	**U[g]**	
Scheduled Day	**Day -2 to 1**	**Day 1**	**Day 2-3**	**Day 3-14**	**Day 5-14**	**7-14 days after EOT**	**7-14 days after EFU**	**28 days post-randomization**	**DC**	
Scheduling Window	**≤48 hr pre-randomization**	**NA**	**NA**	**≤24 hr post-final IV dose**	**≤24 hr post-final dose**	**NA**	**NA**	**+3 days**	**NA**	
Serum β-hCG (female participants of childbearing potential only)	X						X		X	Rapid urine β-HCG may be used for screening, but, if positive, the result must be confirmed by central laboratory serum β-HCG and the participant must be discontinued.

Study Period	**Screening**	**Intervention**				**Follow-up: up to 42 days post-randomization**			**DC**	**Notes**
Visit Number/Title	**1 Screening[a]**	**2 Day 1[b]**	**3 OTX[b]**	**4 EOIV[c] (oral switch only)**	**5 EOT[d] (all)**	**6 EFU[e]**	**7 LFU[e]**	**TC[f]**	**U[g]**	
Scheduled Day	**Day -2 to 1**	**Day 1**	**Day 2-3**	**Day 3-14**	**Day 5-14**	**7-14 days after EOT**	**7-14 days after EFU**	**28 days post-randomization**	**DC**	
Scheduling Window	**≤48 hr pre-randomization**	**NA**	**NA**	**≤24 hr post-final IV dose**	**≤24 hr post-final dose**	**NA**	**NA**	**+3 days**	**NA**	
Hematology	X	X	X	X	X	X			X	For screening, the most recent local laboratory results available ≤48 hr prior to randomization may be used (repeat testing not needed on Day 1). See Table 4 for blood collection in neonates. Follow-up safety laboratory tests can be taken at either EFU or LFU through 14 days after EOT.
Chemistry	X	X	X	X	X	X			X	
Urinalysis	X	X	X	X	X	X			X	
Meningitis Evaluation (Participants <3 months of age)	X									Investigator assessment of absence of meningitis must be documented on the appropriate source documents.

Study Period	**Screening**	**Intervention**				**Follow-up: up to 42 days post-randomization**			**DC**	**Notes**
Visit Number/Title	**1 Screening[a]**	**2 Day 1[b]**	**3 OTX[b]**	**4 EOIV[c] (oral switch only)**	**5 EOT[d] (all)**	**6 EFU[e]**	**7 LFU[e]**	**TC[f]**	**U[g]**	
Scheduled Day	**Day -2 to 1**	**Day 1**	**Day 2-3**	**Day 3-14**	**Day 5-14**	**7-14 days after EOT**	**7-14 days after EFU**	**28 days post-randomization**	**DC**	
Scheduling Window	**≤48 hr pre-randomization**	**NA**	**NA**	**≤24 hr post-final IV dose**	**≤24 hr post-final dose**	**NA**	**NA**	**+3 days**	**NA**	
AE/SAE Monitoring		← Daily during IV study intervention →				X	X		X	Monitor for AEs daily during IV study intervention, at EOIV (if applicable), at EOT, and through 14 days after completion of all study intervention (IV or IV then oral). Any SAE brought to the attention of the investigator outside 14 days post-EOT must be reported immediately to the Sponsor if considered drug related.
Local Infusion Tolerability Monitoring		← Daily during IV study intervention →							X	Monitor for local infusion tolerability AEs daily during IV study intervention.

Study Period	**Screening**	**Intervention**				**Follow-up: up to 42 days post-randomization**			**DC**	**Notes**
Visit Number/Title	**1 Screening[a]**	**2 Day 1[b]**	**3 OTX[b]**	**4 EOIV[c] (oral switch only)**	**5 EOT[d] (all)**	**6 EFU[e]**	**7 LFU[e]**	**TC[f]**	**U[g]**	
Scheduled Day	**Day -2 to 1**	**Day 1**	**Day 2-3**	**Day 3-14**	**Day 5-14**	**7-14 days after EOT**	**7-14 days after EFU**	**28 days post-randomization**	**DC**	
Scheduling Window	**≤48 hr pre-randomization**	**NA**	**NA**	**≤24 hr post-final IV dose**	**≤24 hr post-final dose**	**NA**	**NA**	**+3 days**	**NA**	
Review of Clinical Signs and Symptoms of Infection (associated with both primary and any secondary bacterial infection sites)		← Daily during IV study intervention →				X	X		X	Presence/absence of infection-specific clinical signs and symptoms will be reviewed daily during IV study intervention, and at the EOIV (as applicable) and EOT visits. Table 5.
Infection Source Control Review		X	X	X	X				X	Document source control information per the infection type on the appropriate eCRF.
O_2 Saturation (HABP/VABP only)		← Daily during IV study intervention →				X	X		X	PaO_2/FiO_2 ratio should also be recorded if available.

Study Period	**Screening**	**Intervention**				**Follow-up: up to 42 days post-randomization**			**DC**	**Notes**
Visit Number/Title	**1 Screening[a]**	**2 Day 1[b]**	**3 OTX[b]**	**4 EOIV[c] (oral switch only)**	**5 EOT[d] (all)**	**6 EFU[e]**	**7 LFU[e]**	**TC[f]**	**U[g]**	
Scheduled Day	**Day -2 to 1**	**Day 1**	**Day 2-3**	**Day 3-14**	**Day 5-14**	**7-14 days after EOT**	**7-14 days after EFU**	**28 days post-randomization**	**DC**	
Scheduling Window	**≤48 hr pre-randomization**	**NA**	**NA**	**≤24 hr post-final IV dose**	**≤24 hr post-final dose**	**NA**	**NA**	**+3 days**	**NA**	
Chest X-ray (HABP/VABP)		X	If clinically indicated during IV study intervention						X	Perform on Day 1 if a prior chest x-ray or CT was not performed for current infection ≤48 hr prior to randomization. Perform at DC only if clinically indicated. Record relevant radiographic findings on the appropriate eCRF.

Study Period	**Screening**	**Intervention**				**Follow-up: up to 42 days post-randomization**			**DC**	**Notes**
Visit Number/Title	**1 Screening[a]**	**2 Day 1[b]**	**3 OTX[b]**	**4 EOIV[c] (oral switch only)**	**5 EOT[d] (all)**	**6 EFU[e]**	**7 LFU[e]**	**TC[f]**	**U[g]**	
Scheduled Day	**Day -2 to 1**	**Day 1**	**Day 2-3**	**Day 3-14**	**Day 5-14**	**7-14 days after EOT**	**7-14 days after EFU**	**28 days post-randomization**	**DC**	
Scheduling Window	**≤48 hr pre-randomization**	**NA**	**NA**	**≤24 hr post-final IV dose**	**≤24 hr post-final dose**	**NA**	**NA**	**+3 days**	**NA**	
Gram stain, Culture, and Susceptibility Testing										
HABP/VABP: Lower Respiratory Tract (LRT) Specimen for Gram stain, Culture and Susceptibility Testing	X	Collect post-baseline LRT infection-site specimen only from participants who otherwise require a procedure that allows for specimen collection.								Per Appendix 8 – Section 10.8.1, obtain baseline culture prior to initiation of IV study intervention for local laboratory testing and central laboratory analysis of pathogens. Record findings on the appropriate eCRF on the respective study day(s).

Study Period	**Screening**	**Intervention**				**Follow-up: up to 42 days post-randomization**			**DC**	**Notes**
Visit Number/Title	**1 Screening[a]**	**2 Day 1[b]**	**3 OTX[b]**	**4 EOIV[c] (oral switch only)**	**5 EOT[d] (all)**	**6 EFU[e]**	**7 LFU[e]**	**TC[f]**	**U[g]**	
Scheduled Day	**Day -2 to 1**	**Day 1**	**Day 2-3**	**Day 3-14**	**Day 5-14**	**7-14 days after EOT**	**7-14 days after EFU**	**28 days post-randomization**	**DC**	
Scheduling Window	**≤48 hr pre-randomization**	**NA**	**NA**	**≤24 hr post-final IV dose**	**≤24 hr post-final dose**	**NA**	**NA**	**+3 days**	**NA**	
cIAI: Intra-abdominal Specimen for Culture and Susceptibility Testing	X	Collect post-baseline intra-abdominal infection-site specimen only from participants who otherwise require a procedure that allows for specimen collection.								Per Appendix 8 – Section 10.8.2, obtain baseline culture prior to or within 24 hr after initiation of IV study intervention for local laboratory testing and central laboratory analysis of pathogens. Record findings on the appropriate eCRF on the respective study day(s).

Study Period	**Screening**	**Intervention**				**Follow-up: up to 42 days post-randomization**			**DC**	**Notes**
Visit Number/Title	**1 Screening[a]**	**2 Day 1[b]**	**3 OTX[b]**	**4 EOIV[c] (oral switch only)**	**5 EOT[d] (all)**	**6 EFU[e]**	**7 LFU[e]**	**TC[f]**	**U[g]**	
Scheduled Day	**Day -2 to 1**	**Day 1**	**Day 2-3**	**Day 3-14**	**Day 5-14**	**7-14 days after EOT**	**7-14 days after EFU**	**28 days post-randomization**	**DC**	
Scheduling Window	**≤48 hr pre-randomization**	**NA**	**NA**	**≤24 hr post-final IV dose**	**≤24 hr post-final dose**	**NA**	**NA**	**+3 days**	**NA**	
cUTI: Urine Specimen for Culture with Colony Count and Susceptibility Testing	X	X		X	X	X	X		X	Per Appendix 8 - Section 10.8.3, collect baseline urine culture prior to initiation of IV study intervention on Day 1. Per Section 8.2.3.1.3, collect post-baseline only from participants able to provide a clean specimen (repeat catheterization not required). All samples will be used for local laboratory testing and central laboratory analysis of pathogens. Record findings on the appropriate eCRF on the respective study day(s).

Study Period	**Screening**	**Intervention**				**Follow-up: up to 42 days post-randomization**			**DC**	**Notes**
Visit Number/Title	**1 Screening[a]**	**2 Day 1[b]**	**3 OTX[b]**	**4 EOIV[c] (oral switch only)**	**5 EOT[d] (all)**	**6 EFU[e]**	**7 LFU[e]**	**TC[f]**	**U[g]**	
Scheduled Day	**Day -2 to 1**	**Day 1**	**Day 2-3**	**Day 3-14**	**Day 5-14**	**7-14 days after EOT**	**7-14 days after EFU**	**28 days post-randomization**	**DC**	
Scheduling Window	**≤48 hr pre-randomization**	**NA**	**NA**	**≤24 hr post-final IV dose**	**≤24 hr post-final dose**	**NA**	**NA**	**+3 days**	**NA**	
Blood Specimen for Culture and Susceptibility Testing	As clinically indicated, prior to the initiation of IV study intervention		As clinically indicated or, if prestudy blood culture was positive, repeat until negative on a subsequent culture							If performed, record on the appropriate eCRF.
Efficacy Evaluation										
Survival Assessment						28-day survival assessed on Day 28 at either the EFU or LFU visit or by telephone call on Day 28 (+3 days) post-randomization				
Clinical Response Assessment				X	X	X	X		X	Investigator assessment for presence/absence of infection-specific clinical signs and symptoms at the indicated visits compared with baseline. Table 6 and Table 7.

Study Period	**Screening**	**Intervention**				**Follow-up: up to 42 days post-randomization**			**DC**	**Notes**
Visit Number/Title	**1 Screening[a]**	**2 Day 1[b]**	**3 OTX[b]**	**4 EOIV[c] (oral switch only)**	**5 EOT[d] (all)**	**6 EFU[e]**	**7 LFU[e]**	**TC[f]**	**U[g]**	
Scheduled Day	**Day -2 to 1**	**Day 1**	**Day 2-3**	**Day 3-14**	**Day 5-14**	**7-14 days after EOT**	**7-14 days after EFU**	**28 days post-randomization**	**DC**	
Scheduling Window	**≤48 hr pre-randomization**	**NA**	**NA**	**≤24 hr post-final IV dose**	**≤24 hr post-final dose**	**NA**	**NA**	**+3 days**	**NA**	
Microbiological Response Assessment				X	X	X	X		X	Investigator assessment of participants with a post-baseline infection-site specimen (as clinically appropriate) for microbiological response at the indicated visits. Table 8 and Table 9.

Study Period	**Screening**	**Intervention**				**Follow-up: up to 42 days post-randomization**			**DC**	**Notes**
Visit Number/Title	**1 Screening[a]**	**2 Day 1[b]**	**3 OTX[b]**	**4 EOIV[c] (oral switch only)**	**5 EOT[d] (all)**	**6 EFU[e]**	**7 LFU[e]**	**TC[f]**	**U[g]**	
Scheduled Day	**Day -2 to 1**	**Day 1**	**Day 2-3**	**Day 3-14**	**Day 5-14**	**7-14 days after EOT**	**7-14 days after EFU**	**28 days post-randomization**	**DC**	
Scheduling Window	**≤48 hr pre-randomization**	**NA**	**NA**	**≤24 hr post-final IV dose**	**≤24 hr post-final dose**	**NA**	**NA**	**+3 days**	**NA**	
Pharmacokinetics/Pharmacodynamics/ Biomarkers										
Plasma Pharmacokinetic Sampling for relebactam, imipenem, and cilastatin assay (only participants receiving IMI/REL)		X	X							Blood samples for PK analysis will be collected on Day 1 at 3 time points: (1) 30 min prior to start of first dose of IV study intervention; (2) within 10 minutes after the end of the first infusion; and (3) 2 to 6 hr after start of first infusion; and once at the OTX visit on Day 2 OR 3 at 2 to 6 hr after start of any infusion that day.

AE=adverse event; β-hCG=β-human chorionic gonadotropin; cIAI=complicated intra-abdominal infection; CrCl=creatinine clearance; CT=computed tomography; cUTI=complicated urinary tract infection; DC=discontinuation from the study; eCRF=electronic case report form; EFU=Early Follow-up; EOIV=end of IV therapy; EOT=End of Therapy; HABP/VABP=hospital-acquired or ventilator-associated bacterial pneumonia; hr=hours; IMI/REL=imipenem/cilastatin/relebactam (MK-7655A); IRT=interactive response technology; IV=intravenous; LFU=Late Follow-up; LRT=lower respiratory tract; min=minutes; NA=not applicable; OTX=on therapy; PaO_2/FiO_2 ratio=ratio of partial pressure of oxygen to the fraction of inspired oxygen; PK=pharmacokinetic; SAE=serious adverse event; TC=telephone call; U=unscheduled visit.

[a] Screening procedures must be completed within 48 hours prior to randomization.

[b] Participants who receive IMI/REL will have blood sampling for PK analysis on 2 days during the study: on Day 1 (at the 3 time points indicated) and at the OTX visit (at the 1 time point indicated) on Day 2 OR 3. The OTX and EOIV visits may be combined if both occur on Day 3.

[c] Visit 4 (EOIV) will occur only in participants with cIAI or cUTI whom the investigator deems eligible to switch to oral antibacterial therapy after completion of at least 3 days of IV study intervention based on the participant's clinical condition (see Section 8.1.8.1.2 for the oral switch criteria). The list of acceptable oral switch options is provided in Table 2. If performed, the EOIV visit must occur ≤24 hr after the last IV dose. The OTX and EOIV visits may be combined if both occur on Day 3.

[d] The total duration of all study intervention (IMI/REL group or active control group) must be a minimum of 5 days (cIAI and cUTI, IV alone or IV then oral, of which the first 3 days must be IV before optional oral switch) or 7 days (HABP/VABP, IV alone) up to a maximum of 14 days (IV alone or IV then oral). Participants with bacteremia or *Pseudomonas aeruginosa* infection should receive 14 days of antibacterial therapy. Participants with cIAI or cUTI who switch to oral therapy will have the EOT visit ≤24 hr after the last oral dose up to a maximum of 14 days of all study intervention (IV then oral). For all participants, EOT is the end of all study intervention and the EOT visit must occur ≤24 hours after completion of the last IV or oral dose. Extension beyond 14 days requires Sponsor approval (see Section 4.3.3).

[e] The EFU visit will occur 7 to 14 days after EOT and the LFU visit will occur 7 to 14 days after the EFU visit. EOT is the end of all study intervention (IV or IV then oral).

[f] A telephone call will be made on Day 28-31 post-randomization if the EFU and LFU visits take place prior to Day 28.

[g] Discontinuation procedures are to be performed for all participants who discontinue from any study intervention; ie, those who discontinue study intervention or withdraw from the study at any point after the initiation of IV study intervention.

2 INTRODUCTION

2.1 Study Rationale

This is the second study in support of the pediatric development of IMI/REL (imipenem/cilastatin/relebactam, MK-7655A) for the treatment of bacterial infections caused by gram-negative bacteria, including HABP/VABP, cIAI, and cUTI, in patients who may be infected with carbapenem-resistant gram-negative bacteria.

The goals of this study are to gain additional safety data for IMI/REL in pediatric patients, to confirm dose recommendations derived from the first pediatric study (MK-7655A-020), and to describe efficacy in the pediatric population.

2.2 Background

The FDC of imipenem, cilastatin, and REL was approved as RECARBRIO™ by the US FDA on 16 JUL 2019 for use in patients 18 years of age and older who have limited or no alternative treatment options for the treatment of cUTI, including pyelonephritis, caused by the following susceptible gram-negative microorganisms: *Enterobacter cloacae, Escherichia coli, Klebsiella aerogenes, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* and for the treatment of cIAI caused by the following susceptible gram-negative microorganisms: *Bacteroides caccae, Bacteroides fragilis, Bacteroides ovatus, Bacteroides stercoris, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Fusobacterium nucleatum, Klebsiella aerogenes, Klebsiella oxytoca, Klebsiella pneumoniae, Parabacteroides distasonis,* and *P. aeruginosa*. Refer to the IB for detailed background information on REL (relebactam, MK-7655) and IMI/REL (imipenem/cilastatin/relebactam, MK-7655A) and to the PRIMAXIN® USPI [U.S. Prescribing Information 2017] or TIENAM® SPC (ex-US) [Summary of Product Characteristics 2011] for background information on IMI (imipenem/cilastatin).

2.2.1 Pharmaceutical and Therapeutic Background

β-lactam antibacterials (penicillins, cephalosporins, carbapenems, and monobactams) are among the most frequently used antimicrobial agents in clinical practice. The continuing development of resistance to these β-lactam antibacterials poses an ongoing threat to the clinical utility of all β-lactams. The production of β-lactamases is the most important resistance mechanism among gram-negative bacteria. Therefore, there is an urgent need for new BLIs that can be combined with existing β-lactam antibacterials to protect against hydrolysis by 1 or more of the 4 classes (A, B, C, and D) of β-lactamase enzymes.

Pediatric patients are particularly vulnerable to infections caused by drug resistant gram-negative pathogens due to the few broad-spectrum antibacterials approved for use in pediatric patients. For treatment of carbapenem-resistant Enterobacteriaceae infections in pediatric patients, for example, there are few treatment alternatives; these include aminoglycosides, fluoroquinolones, trimethoprim-sulfamethoxazole, fosfomycin, and nitrofurantoin (mostly for treatment of uncomplicated UTI). Many of these antibacterials have limitations, such as

the rapid emergence of resistance when aminoglycosides are used as single agents for bacteremia and the caution that needs to be exercised when prescribing fluoroquinolones to pediatric patients due to osteoarticular side-effects observed in animal models as well as pediatric patients [Hsu, A. J. 2014] [U.S. Food and Drug Administration 2018].

REL is a parenteral (IV), small-molecule BLI that has been developed for administration as an FDC in a single vial with imipenem/cilastatin (IMI) for the treatment of infections caused by carbapenem-resistant, gram-negative bacteria. The FDC of imipenem/cilastatin/relebactam (MK-7655A) is referred to as IMI/REL.

REL represents a new generation of BLIs to combat evolving antibacterial resistance and to maintain the usefulness of the β-lactam class of antibacterials. REL is an inhibitor of Ambler class A and class C β-lactamases. This BLI is highly potent for AmpC, a common class C β-lactamase encountered in many bacteria, most predominantly *P. aeruginosa*. REL is also active against the class A β-lactamases, including the KPC present in some Enterobacteriaceae, including Klebsiella strains. The IMI/REL β-lactam/BLI combination builds on a long history of pediatric safety and efficacy of IMI (Section 2.2.2) and its broad spectrum of activity.

2.2.2 Preclinical and Clinical Studies

Details of preclinical and clinical studies are described in the IB. Overall, the preclinical toxicity profile observed with REL supported continuation of clinical studies with this compound. In addition, there were no REL-related findings in a 1-month juvenile toxicity study conducted in rats, up to 450 mg/kg/day (maximum feasible dose) administered subcutaneously (postnatal Day 14 to 34) or intravenously (postnatal Day 35 to 56/57) at 65, 200, or 450 mg/kg/day (~6-fold the clinical exposure).

REL has been evaluated in adults either alone or in combination with IMI (as IMI + REL or the FDC IMI/REL) in 10 completed Phase 1 studies, 2 completed Phase 2 studies (MK-7655 003 [PN003] and MK-7655-004 [PN004]), and 4 completed Phase 3 studies (MK-7655A-013 [PN013], and MK-7655A-014 [PN014], MK-7655A-016 [PN016], MK-7655A-017 [PN017]). The details and results of these studies are described in the IB [IB Edition 14 2021]. A brief summary of the results is as follows:

- In the Phase 2 studies, coadministration of 500 mg IMI and either 125 mg or 250 mg of REL was noninferior to treatment with 500 mg IMI alone in the treatment of cUTI (PN003) and cIAI (PN004) in a population in which most participants had an imipenem-susceptible infection.
- In the Phase 3 studies, the FDC IMI/REL was at least as efficacious as colistin (in the form of colistimethate sodium) + IMI for the treatment of imipenem-nonsusceptible and imipenem/REL- and colistin-susceptible bacterial infections (specifically HABP/VABP, cIAI, and cUTI) (PN013) and IMI/REL (500 mg/250 mg) q6h IV was generally well tolerated, with a favorable safety profile, and was an effective treatment for Japanese participants with cIAI or cUTI (PN017). In a study of safety and efficacy of IMI/REL compared to PIP/TAZ in 274 participants with HABP/VABP, IMI/REL was noninferior

to PIP/TAZ for the primary endpoint of all-cause mortality through Day 28 and the safety profile of IMI/REL was comparable to PIP/TAZ (PN016).

- Safety data from the 835 unique participants exposed to REL across the adult clinical development program demonstrate that IMI/REL is well tolerated in healthy participants and in patients with serious bacterial infections, including critically ill patients and those infected with carbapenem resistant gram-negative bacteria. IMI/REL has a favorable safety profile that is similar to that of IMI alone and has a more favorable safety profile than that of colistin.

There is 1 completed pediatric clinical study with MK-7655A at this time (MK-7655A-020 [PN020]). PN020 was an open-label, single-dose study to evaluate the PK, safety, and tolerability of IMI/REL in pediatric participants from birth to less than 18 years of age with proven or suspected gram-negative infections. The main objective of the study was to determine safe starting doses for pediatric cohorts that yielded exposures associated with efficacy in adults.

PN020 showed that imipenem, REL, and cilastatin exhibited approximately dose-proportional PK across Cohorts 1 to 5; and both imipenem and REL exceeded protocol-defined PK targets across Cohorts 1 to 5. A single dose of IV IMI/REL was generally well tolerated in pediatric participants from birth to less than 18 years of age and no safety concerns were identified.

There has been considerable experience with the use of IMI (imipenem/cilastatin) in both adults and pediatric patients since its initial approval over 30 years ago. The 2 pediatric clinical studies conducted by the Sponsor were open-label studies to evaluate the efficacy, safety, tolerability, and PK of IMI in approximately 233 hospitalized pediatric participants of 3 months to 12 years of age with serious bacterial infections, including respiratory tract, intra-abdominal, and urinary tract infections. IMI was efficacious and generally well tolerated in both pediatric studies.

2.2.3 Ongoing Clinical Studies

The current study in pediatric participants, MK-7655A-021, abbreviated as PN021, is the only ongoing clinical study.

2.2.4 Information on Other Study-related Therapy

Multiple active control regimens will be permitted in this study, as listed in Appendix 9 (see Section 4.2.3 on the rationale for their selection), consistent with real-world practice for the treatment of HABP/VABP, cIAI, and cUTI in pediatric patients. The selected regimen will ultimately depend on the needs of the patient per local standard of care.

2.2.4.1 Optional Oral Switch (cIAI, cUTI)

In the treatment of cIAI and of cUTI, it is common practice to switch from parenteral to oral antibacterials when the patient is afebrile and/or improving [Becknell, B., et al 2015] [Grabe, M., et al 2013] [Stein, R., et al 2015], [Zorc, J. J., et al 2005]. For participants with cIAI or

cUTI, this study allows the investigator to opt to switch the participant to oral antibacterial study intervention after at least 3 days of IV study intervention, based on the participant's clinical condition. See Section 8.1.8.1.2 for investigator criteria for determining whether the participant's clinical condition warrants switch to oral antibacterial therapy for treatment of cIAI or cUTI in this study.

The acceptable oral switch options listed in Appendix 9 are common oral antibacterials with appropriate activity against the most common gram-negative pathogens encountered in cIAIs and cUTIs, respectively.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

Efficacy data from the Phase 2 and Phase 3 adult development program have demonstrated that IMI/REL is noninferior to IMI alone in the treatment of cUTI and cIAI, and is at least as efficacious as colistin for the treatment of gram-negative, imipenem-nonsusceptible, colistin-susceptible bacterial infections (specifically HABP/VABP, cIAI, and cUTI). The pathogenesis and microbiology of these diseases are similar in pediatric patients and in adults.

In this study, participants will either receive multiple IV infusions of IMI/REL or standard-of-care treatment (Section 4.1). The risks of administration of multiple doses of IMI/REL are considered to be minimal. IMI has a well-established safety and tolerability profile among pediatric patients, both from the pediatric development program and from decades of clinical use for serious bacterial infections. Furthermore, there are no significant or excessive adverse effects observed among other preclinical or clinical studies involving REL or IMI/REL to date (see Section 2.2.2). There is no evidence of additional risk posed by the addition of REL to IMI; the safety profile of the combination is similar to that of IMI alone.

Obtaining blood samples for PK analysis does pose a small risk, which is minimized by imposing blood sampling volume limits and reducing the frequency of sampling (Table 4). Although more frequent, the proposed study procedures described in Section 1.3 – SoA are generally standard procedures performed for the target patient population (eg, chemistry and hematology measurements).

Additional details regarding specific benefits and risks for participants in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

There are no formal statistical hypotheses to be evaluated in this study.

The following objectives and endpoints will be evaluated in pediatric participants from birth to less than 18 years of age with confirmed or suspected gram-negative bacterial infection involving 1 of 3 primary infection types: HABP/VABP, cIAI, or cUTI:

Primary Objective	**Primary Endpoint**
To evaluate the safety and tolerability of IMI/REL (imipenem/cilastatin/relebactam) from the first dose of intravenous (IV) study intervention through 14 days after the end of therapy (EOT)	Adverse events (AEs) IV study intervention discontinuations due to AEs
Secondary Objectives	**Secondary Endpoints**
To evaluate the efficacy of IMI/REL by assessing all-cause mortality at Day 28 postrandomization and clinical and microbiological response at the EOT, Early Follow-up (EFU, 7 to 14 days after EOT), and Late Follow-up (LFU, 7 to 14 days after EFU) visits	All-cause mortality Favorable clinical response Favorable microbiological response
To characterize the PK profile of imipenem and relebactam following administration of IMI/REL	Plasma concentrations of imipenem and relebactam $AUC_{0\text{-}24hr}$ and C_{eoi} for imipenem and relebactam %T>MIC for imipenem
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
To evaluate the efficacy of IMI/REL by assessing clinical and microbiological response at the End of IV (EOIV) visit (for participants who switch to oral therapy) To evaluate the efficacy of IMI/REL by assessing by-pathogen microbiological response at the EOIV (for participants who switch to oral therapy), EOT, EFU, and LFU visits	Favorable clinical response Favorable microbiological response Favorable by-pathogen microbiological response

4 STUDY DESIGN

4.1 Overall Design

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 of the SoA. Details of each procedure are provided in Section 8.

This is a randomized, active-controlled, parallel-group, multi-site, open-label study of IMI/REL in pediatric participants from birth to less than 18 years of age with confirmed or suspected gram-negative bacterial infection. Participants with HABP/VABP, cIAI, or cUTI will be randomized in a 3:1 ratio to receive IMI/REL or active control. Participants will be stratified by age group and infection type prior to randomization (see Section 6.3.2).

Approximately 140 participants will be enrolled to target having 132 participants (approximately 99 in the IMI/REL group and 33 in the active control group) included in the safety population (ie, who received at least 1 dose of IV study intervention).

Five pediatric age cohorts will be evaluated in the study as follows, with the following minimum or maximum number of participants enrolled in each:

- Age Cohort 1: Adolescents (12 to <18 years) - No more than 12 participants
- Age Cohort 2: Older Children (6 to <12 years) - At least 20 participants
- Age Cohort 3: Younger Children (2 to <6 years) - At least 20 participants
- Age Cohort 4: Infants and Toddlers (3 months to <2 years) - At least 28 participants
- Age Cohort 5: Neonates and Young Infants (birth to <3 months) - At least 28 participants

Three infection types will be evaluated in the study as follows. As differences in the distribution of infection types within each age cohort are likely, a balance of infection types across age cohorts is unlikely to be achievable; therefore, an IRT system will be used to meet the following enrollment targets:

- At least 28 participants with any of the following infections: HABP/VABP or cIAI.
- cIAI - At least 10% of participants with cIAI have a diagnosis other than complicated appendicitis.
- cUTI - No more than 48 participants with cUTI in Age Cohorts 3, 4, and 5 combined.

All participants will receive multiple IV doses of either IMI/REL or active control for a total duration of all study intervention of a minimum of 5 days (cIAI and cUTI, IV alone or IV then oral, of which at least 3 days must be IV alone before optional oral switch) or 7 days (HABP/VABP, IV alone) up to a maximum of 14 days (IV alone or IV then oral). Extension of study therapy beyond 14 days requires Sponsor approval as described in Section 4.3.3. Doses and treatment regimens are specified in Table 3. For IMI/REL, adolescent participants

(Age Cohort 1) will receive the approved adult dose and participants <12 years of age (Age Cohorts 2-5) will receive weight-based dosing, not to exceed the adult dose.

Safety, tolerability, efficacy, and PK assessments will be conducted during the intervention and follow-up periods as described in Figure 1 and the SoA (Section 1.3). Study visits will be performed at randomization (Day 1), OTX, at the end of IV therapy (EOIV, only for participants who switch to oral therapy), and at the EOT. The EOT is the end of all study intervention (IV alone or IV then oral). Following the completion of all study intervention, participants will be evaluated 7 to 14 days after EOT (at the EFU visit) and 7 to 14 days after the EFU visit (at the LFU visit). The investigator may decide to switch participants with cIAI or cUTI to oral antibacterial therapy based on the participant's clinical condition (see the oral switch criteria in Section 8.1.8.1.2) after a minimum of 3 days of IV study intervention; these participants will have an EOIV visit (see the SoA) and complete a total duration of all study intervention (IV then oral) of a minimum of 5 days up to a maximum of 14 days. All participants will have a Day 28 post-randomization survival assessment, which may be performed on the same day as the EFU or LFU visit or as a separate telephone contact. In addition, all deaths that occur during the study period will be reported as part of routine safety assessment.

Safety and tolerability will be monitored periodically throughout the study and at the planned interim analysis (described below) by an eDMC in conjunction with the Sponsor EOC as described in Section 9.7 and Appendix 1 - Section 10.1.4. The enrollment strategy is described in Figure 2. For Age Cohorts 1, 2, and 3, enrollment will be initiated in parallel. To assess whether the safety and tolerability profile is acceptable overall and for each age cohort and to confirm the proposed initial doses for Age Cohorts 4 and 5, an interim analysis will be performed when at least 20 participants in each of Age Cohorts 2 and 3 have complete data available (all complete data available from Age Cohorts 1, 2, and 3 will be reviewed at this time). No formal efficacy analyses will be conducted for eDMC review; however, PK and/or efficacy data will be provided to the eDMC on request to support benefit-to-risk evaluation. Once the proposed initial doses for Age Cohorts 4 and 5 are confirmed based on the findings from internal interim review, as described in Section 9.7, enrollment in Age Cohorts 4 and 5 will begin in parallel. Enrollment in Age Cohorts 1, 2, and 3 will continue beyond the interim review up to a maximum of approximately 84 participants across Age Cohorts 1, 2, and 3, until at least 28 participants each in Age Cohorts 4 and 5 have final data available and the target of 132 participants across all age cohorts in the safety analysis population has been achieved.

An interim analysis to assess safety, tolerability, efficacy, and PK may be performed when final data from Age Cohorts 1 to 3 are available. The final analysis of aggregated safety, tolerability, efficacy, and PK data from Cohorts 1 through 5 will be performed when enrollment in Age Cohorts 4 and 5 has completed and the total enrollment has been achieved.

If needed, dose modifications will be determined and communicated as described in Section 6.6 – Dose Modification.

Each participant will remain in the study for up to 44 days from the time the participant's legally acceptable representative provides documented informed consent through the final

contact. This includes a screening phase of up to 2 days before receiving the first dose of IV study intervention, up to 14 days of study intervention (IV alone or IV then oral), and up to 28 days of follow-up after the last IV or oral dose of study intervention.

4.2 Scientific Rationale for Study Design

This study is randomized to minimize bias. A 3:1 randomization ratio has been selected to gain greater experience with IMI/REL and to maximize the opportunity to assess safety and efficacy. Randomization is stratified by age and by infection type for balanced distribution across age cohorts and infection types. The oldest 3 age cohorts (Age Cohorts 1, 2, and 3) will be studied in parallel. Enrollment in the 2 youngest age cohorts (Age Cohorts 4 and 5) will be initiated after completion of the internal interim review of aggregated safety, tolerability, efficacy, and PK data from Age Cohorts 1, 2, and 3, and confirmation of doses.

A comparative design is used for descriptive analysis of safety and efficacy data and to confirm dose selection for all age cohorts based on PN020 results. As described in Section 4.2.3, multiple active control regimens are permitted; as such, this is an open-label study, as blinding of multiple active control regimens is not feasible and the need to administer placebo infusions is avoided.

There is no formal statistical testing of hypotheses in this study. Instead, the goal is to provide estimates of important safety, efficacy, and PK endpoints in the overall study population as well as within the different age cohorts.

4.2.1 Rationale for Study Population

Participants with 1 of 3 primary infection types (HABP/VABP, cUTI, or cIAI) will be enrolled in this study. These 3 infection types are consistent with the infections studied in the adult development program for IMI/REL. It is well documented that the lungs, abdomen, and urinary tract are some of the most common sites of infection in patients with MDR infections, including CR, gram-negative infections (*P. aeruginosa* and KPC), as well as healthcare-associated infections [Markou, Nikolaos, et al 2003], [Reina, R., et al 2005], [Falagas, M. E., et al 2005], [Pintado, V., et al 2008], [Garnacho-Montero, J., et al 2003], [Cheng, C.-Y., et al 2010], [Kallel, H., et al 2007], [Hachem, Ray Y., et al 2007], [Bader, M. S., et al 2010]. In addition, HABP/VABP, cUTI, and cIAI are important healthcare-associated infections in pediatric patients, as evidenced by the following:

- Among ventilated PICU patients, VABP occurs in 3% to 9% of patients [Elward, A. M., et al 2002] [Patria, M. F. 2013] [Roeleveld, P. P., et al 2011]. Among neonatal ICU patients, pneumonia is the second most common healthcare-associated infection, occurring at a rate of 0.2 to 1.7 per 1000 ventilator days, with higher rates in the smallest weight subsets [Hooven, T. A. 2014] [Dudeck, M. A., et al 2013].
- Among patients with cIAI, appendicitis as a single entity occurs at an overall rate of 10.9 cases per 10,000 population for all ages, and at a rate of 12.9 cases per 10,000 population for the age group <15 years of age [DeFrances, C. J., et al 2007]. Appendicitis is more common in pediatric and young adult populations compared with older adults

[Addiss, D. G., et al 1990] [Andersen, S. B., et al 2009]; it occurs in 7% of the population over their lifetime [Addiss, D. G., et al 1990].

- Catheter-associated urinary tract infection (CAUTI) is a subset of cUTI and is the most common type of nosocomial infection, accounting for 40% of hospital-acquired infections. The Pediatric Prevention Network reported the US point prevalence of pediatric CAUTI in PICUs to be 13.3 per 1000 urinary catheter days [Davis, K. F., et al 2014] [Grohskopf, L. A., et al 2002].

This study does not limit enrollment to participants with CR infections. In the pivotal Phase 3 study PN013, adult participants were required to have screening susceptibility testing and confirmed CR infection for study entry. However, in this study, the primary objective is to evaluate safety and tolerability in pediatric participants, and no formal statistical testing will be performed for the efficacy endpoints. Since efficacy against infections due to resistant pathogens is not being evaluated, confirmed CR infection is not required for study entry.

4.2.1.1 Rationale for Exclusion of Patients With Renal Impairment

Patients with renal impairment are excluded from participating in this study (Section 5.2).

Imipenem, cilastatin, and REL are all known to be substantially excreted by the kidney, and the risk of toxic reactions to them may be greater in patients with impaired renal function. Please refer to the PRIMAXIN® (imipenem/cilastatin) USPI [U.S. Prescribing Information 2017] or TIENAM® Summary of Product Characteristics (ex-US) [Summary of Product Characteristics 2011] and to the IB on dose adjustment and detailed considerations regarding IMI/REL use in participants with renal impairment. IMI is not recommended in pediatric patients weighing <30 kg with renal impairment, as no data are available on use in this population, and there are no dosing recommendations for pediatric patients with renal impairment in the USPI.

Patients requiring hemodialysis are likewise excluded from this study, as are patients requiring peritoneal dialysis, for whom there is inadequate information to recommend usage. In adults, patients with CrCl <90 mL/min (calculated using the Cockcroft-Gault equation) require dosage reduction of IMI. In patients with CrCl <30 to ≥15 mL/min, there may be an increased risk of seizures. Patients with CrCl <15 mL/min should not receive IMI unless hemodialysis is instituted within 48 hours. For patients on hemodialysis, IMI is recommended only when the benefit outweighs the potential risk of seizures. Administration of IMI to such patients would require individual patient-level evaluation of the risk/benefit of treatment (ie, the same rule cannot be applied to all study participants) [U.S. Prescribing Information 2017].

4.2.1.2 Rationale for Exclusion of Patients With Meningitis

Participants less than 3 months of age will be enrolled in this study only after the investigator rules out meningitis by performing an LP with CSF culture (if clinically indicated per local standard-of-care) or by other standard-of-care procedures or clinical assessments (see Section 5.2 and Section 8.3.4). Neonates and young infants less than 3 months of age with fever are generally treated empirically for meningitis until it can be ruled out

[Kadish, H. A., et al 2000] [Ferrera, P. C., et al 1997] [Bonadio, W. A., et al 1993] [Bachur, R. G. 2001] [Bedetti, L., et al 2018]. IMI is not indicated in pediatric patients with CNS infections, including meningitis, because of the risk of seizures [U.S. Prescribing Information 2017]. The investigator's assessment of the absence of meningitis must be documented on the source documents at the time of screening. This study excludes participants less than 3 months of age who have had more than 72 hours of prior empiric antibacterial treatment for suspected meningitis prior to initiation of IV study intervention. This 72-hour window for this age cohort allows time for LP with CSF culture results to rule out meningitis (see Section 8.3.4). Exclusion of meningitis is consistent with the well-established clinical management of young infants with serious bacterial infections and guidance on the treatment of bacterial infections [European Medicines Agency 2013], nosocomial pneumonia [West, M., et al 2003], HABP/VABP, [Food and Drug Administration 2014], cIAI [Food and Drug Administration 2018], and cUTI [Food and Drug Administration 2018].

4.2.2 Rationale for Endpoints

4.2.2.1 Efficacy Endpoints

A secondary objective of this study is to evaluate the following efficacy endpoints in randomized pediatric participants with HABP/VABP, cUTI, or cIAI:

- All-cause mortality through Day 28 post-randomization
- Clinical response assessed at the EOT, EFU (7 to 14 days after EOT), and LFU (7 to 14 days after EFU) visits
- Microbiological response assessed at the EOT, EFU, and LFU visits

Exploratory objectives of this study are to evaluate the following efficacy endpoints:

- Clinical response assessed at the EOIV visit (for participants who switch to oral therapy)
- Microbiological response assessed at the EOIV visit (for participants who switch to oral therapy)
- By-pathogen microbiological response assessed at the EOIV visit (for participants who switch to oral therapy) and at the EOT, EFU, and LFU visits (for all participants)

4.2.2.1.1 All-cause Mortality/Survival Status

Survival status (ie, whether the participant is alive or dead) through Day 28 post-randomization will be evaluated for all participants in support of the key secondary objective.

Evaluation of mortality is appropriate in this study population given the severity of illness in hospitalized patients who may have acquired MDR gram-negative bacterial infections and routinely require in-hospital treatment with IV antibacterials. For example, in recently conducted studies in adults with HABP/VABP, approximately 15% of adult participants died despite receiving antibacterial drug therapy [Freire, A. T., et al 2010] [Joshi, M., et al 2006]

[Torres, A., et al 2000] [Chastre, J., et al 2008]. As in adults, HABP/VABP in pediatric patients has been associated with increased mortality and increased hospital and/or ICU length of stay [Foglia, E., et al 2007] [Gupta, S., et al 2015] [Gautam, A., et al 2012] [Patria, M. F. 2013] [Roeleveld, P. P., et al 2011]. Although published data in pediatric populations have been criticized for being unmatched for severity of illness and univariate, they have suggested that pediatric patients with VAP may have excess mortality and length of ICU stay [Foglia, E., et al 2007]; a European epidemiology study of hospital-acquired infections found a mortality rate of 10% in PICU patients with nosocomial infections [Foglia, E., et al 2007] and a US multicenter, prospective study found pediatric patients with VAP to have an unadjusted mortality rate of 10% to 20% [Gupta, S., et al 2015].

A 1-month mortality endpoint has commonly been used for evaluation of efficacy of antibacterial therapy against HABP/VABP [Kollef, M. H., et al 2012] [Chastre, J., et al 2008] [West, M., et al 2003] and against MDR gram-negative infections [Markou, Nikolaos, et al 2003] [Pintado, V., et al 2008] [Cheng, C.-Y., et al 2010]. In addition to assessing all-cause mortality at Day 28, all deaths that occur during the entire study period will be reported as part of routine safety assessment.

4.2.2.1.2 Clinical Response

As in the adult studies, clinical response will be assessed for all participants based on evaluation by the investigator at the time points specified in the SoA. Based on comparison to baseline clinical signs and symptoms of the participant's infection, the investigator will determine the clinical response rating, and the Sponsor will classify the response as "favorable" or "unfavorable" at each visit as described in Section 8.2.2.2 (Table 6 and Table 7).

The evaluation of clinical response at these time points will provide data to characterize the response profile of the test product, relative to the active control. Most cIAI studies evaluate efficacy based on clinical response because secondary microbiological cultures are generally not available. These analyses are routinely performed at the end-of-study therapy and at post-therapy follow-up visits, which is consistent with the time points selected in this study.

4.2.2.1.3 Microbiological Response

As in the adult studies in the IMI/REL development program, microbiological response will be assessed based on each infection-site pathogen isolated in the baseline infection-site culture (ie, by pathogen) for:

- Participants with HABP/VABP or cIAI who require a procedure that allows for specimen collection postbaseline and in whom at least 1 gram-negative baseline pathogen is isolated; and
- Participants with cUTI who are able to provide a clean urine specimen postbaseline and in whom at least 1 gram-negative baseline pathogen is isolated at the minimum colony count specified in the cUTI Microbiology criteria (Appendix 8 - Section 10.8.3).

Assessment of microbiological response (Section 8.2.3.2) will also consider blood pathogens isolated in the baseline blood culture for participants with blood cultures available (Section 8.2.3.1.4).

The investigator will determine the by-pathogen response rating at visits specified in the SoA based on the local laboratory results of infection-site cultures collected for participants at each of these visits, when available, relative to the pathogen(s) isolated at baseline as described in Section 8.2.3.2 (Table 8 and Table 9).

The Sponsor will assess the overall microbiological response (ie, overall microbiological response for the participant based on the response of all pathogens present in the baseline culture) as "favorable" or "unfavorable" for determining participants' microbiological response for the respective infection type in this study.

See Section 8.2.3.1 for details of the infection-site specimen and blood culture procedures.

In participants with cUTI, it is usually feasible to collect appropriate follow-up specimens (ie, urine) at each of the endpoint visits throughout the study. However, collection of respiratory and/or intra-abdominal specimens after initiation of study antibacterials may not be feasible or medically appropriate for participants with HABP/VABP or cIAI, making it difficult to document microbiological eradication in participants with these infections. Therefore, presumed eradication may be inferred when no respiratory or intra-abdominal specimen is available because a participant is deemed clinically improved or cured of the pathogen that was found at the time of study entry.

In participants with HABP/VABP, LRT cultures would preferentially include samples collected from a tracheostomy or endotracheal aspirates, or bronchoscopy specimens. Expectorated or induced sputum samples are also accepted provided the sample does not represent oropharyngeal contamination (ie, sample contains fewer than 10 squamous epithelial cells and greater than 25 neutrophils on low-power microscopy review of the Gram stain).

Most cUTI studies evaluate efficacy based on microbiological eradication of the bacterial pathogens from subsequent urine cultures. Such analyses are routinely performed at the end-of-study therapy and following completion of all antibacterial therapy (usually 1 week and 4 to 6 weeks following completion of all antibacterial therapy). This is consistent with the time points for microbiological response specified in the SoA. Although not typically measured as a primary efficacy outcome in HABP/VABP or cIAI studies, microbiological response will also be measured in participants with these infection types who have post-baseline cultures available (as described above) to allow for further characterization of IMI/REL efficacy.

4.2.2.1.4 Exploratory Endpoint: By-pathogen Microbiological Response

In addition to evaluating microbiological response for each participant who has an acceptable post-baseline infection-site specimen available, microbiological response will also be evaluated separately for each infection-site pathogen isolated in the baseline culture. See Sections 8.2.3 and 8.2.4 for details of the procedures, assessments, ratings (Table 8 and

Table 9), and categories ("favorable" or "unfavorable") for determining participants' by-pathogen microbiological response for the respective infection type in this study.

4.2.2.2 Safety Endpoints

The primary objective of the study is to evaluate the safety and tolerability of IMI/REL from the first dose of IV study intervention through 14 days after completion of all study intervention. The safety and tolerability of IMI/REL (as well as of the active control) will be assessed through descriptive statistics within the safety analysis population for each age cohort by clinical evaluation of AEs and inspection of other safety parameters including local tolerability assessments and standard clinical laboratory evaluations at the time points specified in the SoA. Adverse events are graded and recorded as set out in Section 8.4. Participants may be asked to return for unscheduled visits to perform additional safety monitoring.

4.2.2.3 Pharmacokinetic Endpoints

Another secondary objective of this study is to characterize the PK profile of imipenem and REL following administration of IMI/REL.

At the time points specified in the SoA, only participants randomized to receive IMI/REL will have whole blood samples collected for determination of plasma concentrations of REL, imipenem, and cilastatin. These samples will support further evaluation of the PK profiles of these drugs by confirming that participants achieve expected exposures, and will also aid in further assessment of the clinical relationship between imipenem and REL plasma concentrations and efficacy.

Sparse PK sampling will be performed at 4 time points per participant to minimize the number of samples and blood volume drawn from pediatric participants. The sample at the end of the first infusion on Day 1 will help further characterize the maximum concentration (C_{max}), and each sample during the elimination phase window (Day 1 sample taken 2 to 6 hours after first dose, and the Day 2 to 3 sample) will help characterize the elimination phase. Together, these data will help characterize the entire PK profile using the population PK modeling and confirm the ratio of the free area under the plasma concentration-time curve to the imipenem/REL MIC (fAUC$_{0\text{-}24h}$/MIC) and the percentage of time free imipenem concentration is above the imipenem/REL MIC (% fT>MIC) estimation for REL and imipenem, respectively. REL and imipenem PK data will be added to existing pediatric PK data from PN020 to further update the pediatric population PK model. Collecting PK data on multiple days on therapy will also enable capturing any impact of disease status on the PK/dosing of the drugs. See Section 9.4.3 for further details on the PK analysis endpoints.

Based on established literature in the field and data from the adult IMI/REL development program, efficacy of IMI/REL is driven by the % fT>MIC within the dosing interval for imipenem and by fAUC$_{0\text{-}24h}$/MIC for REL. Because the pathogenesis and microbiology of the infections for which IMI/REL is being developed are similar in adult and pediatric populations, the PK targets selected in this study are the same as those for adults.

The goal of the model-based simulations is to confirm that these targets are jointly achieved in a proportion of pediatric participants similarly covered in adults (~90% probability of target attainment) for each age cohort; hence, achieving these targets implies similar efficacy as that obtained in adults. An absolute (mg) or weight-based (mg/kg) dose, whichever is found most suitable for each age cohort, will be selected based on the simulation results.

Plasma concentrations of REL, imipenem, and cilastatin will be determined. As this is an estimation study, no formal statistical testing will be performed for the PK data. The additional REL and imipenem PK data collected in this study will be used to update the pediatric population PK model, based on the adult model, and confirm the adequacy of selected doses. The population PK analysis will be summarized in a separate pediatric population PK modeling and simulation report; the model will then be used in simulations to determine suitable dosing regimens for subsequent and separate pediatric clinical efficacy studies. The PK properties of cilastatin based on data from this study will also be described on an as-needed basis.

4.2.3 Rationale for the Use of Active Controls

Acceptable active control options per local standard of care for each respective infection type are listed by drug class in Table 2 and by generic drug name in Appendix 9 - Protocol-allowed Comparator Medications by Drug Name. The Sponsor considers these options to be clinically appropriate and acceptable active controls with which to evaluate the safety and efficacy of IMI/REL in pediatric participants with HABP/VABP, cIAI, and cUTI.

In contrast to adults, there are no specific guidelines for the treatment of gram-negative bacterial infections, with the exception of cIAI, in the pediatric population, and there is considerable variation in clinical practice across healthcare facilities. Given the variation in practice, as well as geographic differences in epidemiology and the wide variety of pediatric health conditions that may result in the need for mechanical ventilation (ranging from healthy children with traumatic injuries to pediatric patients with multiple complex medical conditions), mandating a single active control regimen would limit study feasibility and would be inconsistent with real-world clinical practice. The selected regimen will ultimately depend on the needs of the patient.

Empiric gram-positive coverage will similarly be left to the investigator's judgment, as IMI/REL has inherent gram-positive coverage due to its IMI component, as do other β-lactam/BLI agents that may be used for HABP/VABP. Coverage for methicillin-resistant *Staphylococcus aureus* (MRSA) should be considered where necessary based on local epidemiology, but will not be required for all participants. Specific considerations for treatment of each infection type are discussed in Section 4.3.3.

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

The initial doses of IMI/REL for Age Cohorts 1 through 3 are as follows:

- Age Cohort 1: 500/250 mg q6h administered as a 60-minute infusion
- Age Cohort 2: 15/7.5 mg/kg q6h administered as a 60-minute infusion
- Age Cohort 3: 15/7.5 mg/kg q6h administered as a 60-minute infusion

These doses were selected based on results from the first 3 age cohorts in PN020 (Section 2.2.3 – Ongoing Clinical Studies). For weight-based dosing for participants <12 years of age (Age Cohorts 2 through 5), the maximum allowed dose is 500/250 mg (or the approved adult dose), as noted in Table 3. The doses of IMI/REL for pediatric participants in Age Cohorts 4 and 5 were selected based on safety, tolerability, and updated PK modeling and simulation analyses, after incorporating observed PK data from Age Cohorts 1 through 3 during the interim review. The doses for Cohorts 4 and 5 were based on pediatric-model-based simulations with the intent of 1) obtaining similar exposures as achieved in adult cUTI/cIAI participants with normal renal function receiving IMI/REL 500/250 mg IV q6h, and 2) ensuring high PTA comparable to adults, and meeting safety margin criteria. The proposed initial doses in the current study were modified as described in Section 6.6 – Dose Modification.

4.3.2 Maximum Dose Exposure for This Study

As described in Section 6.6 – Dose Modification, the doses for each age cohort in this study may be modified based on results of observed safety, tolerability, efficacy, and PK data from the interim review of Age Cohorts 1 through 3. The final pediatric doses will not exceed the dosage studied for adult participants in the Phase 3 studies (ie, maximum single IV dose of IMI/REL 500/250 mg).

4.3.3 Rationale for Dose Interval and Study Design

For participants in the IMI/REL intervention arm, multiple doses of IMI/REL will be administered as a 60-minute IV infusion q6h or q8h, as set out in Table 3. A multiple-dose study design was selected based on the expected clinical use of IMI/REL in both adult and pediatric participants. A short half-life (approximately 30 to 60 minutes) of both imipenem and REL and lack of accumulation of any drug components was observed in adult studies. These properties are expected to be the same in pediatric participants, as supported by interim results from the PN020 single-dose PK study in pediatric participants with confirmed or suspected gram-negative infections.

Appropriate duration of therapy for treatment of pediatric suspected or confirmed gram-negative bacterial infections (HABP/VABP, cIAI, and cUTI) remains controversial, but most guidelines suggest 5 to 14 days of antibacterial therapy. In this study, the total duration of all antibacterial study intervention must be a minimum of 5 days (cIAI and cUTI, IV alone or IV

then oral, of which at least 3 days must be IV alone before optional oral switch) or 7 days (HABP/VABP, IV alone) up to a maximum of 14 days (IV alone or IV then oral). Of note, participants with evidence of concurrent bacteremia or with *P. aeruginosa* infection should receive 14 days of antibacterial treatment. For participants who may require extended durations of treatment (eg, those with suppressed immunity), extension of study intervention beyond 14 days may be allowed with Sponsor approval, as discussed between the Principal Investigator and Sponsor and documented on the Sponsor consultation form.

The intervention duration is consistent with practice guidelines and data from clinical studies. Current clinical practice guidelines suggest limiting treatment of infection types included in this study to 2 weeks. Infectious Diseases Society of America (IDSA) guidelines recommend limiting treatment of HABP/VABP to as little as 1 week, cIAI to less than 1 week for most infections, and CAUTI to less than 2 weeks [Hooton, T. M., et al 2010] [Solomkin, J. S., et al 2010] [Niederman, M. S. 2005] [Dellinger, R. P., et al 2013]. The requirement of at least 3 days (cIAI and cUTI) or 7 days (HABP/VABP) of IV study intervention in this study allows for evaluation of the safety, efficacy, and PK of IMI/REL while minimizing the need for prolonged hospitalization and IV access. Preclinical data for IMI/REL support and the clinical complexity of participants in this study warrants up to 14 days of study intervention. Refer to the IB for more detailed information on preclinical toxicity studies and Sections 4.3.3.1 through 4.3.3.3 below for specific considerations for each of the 3 infection types.

AE data from the pivotal Phase 3 study (PN013) have demonstrated that treatment with the FDC IMI/REL (500 mg/250 mg) q6h for 5 (cUTI and cIAI) or 7 (HABP/VABP) days up to 21 days has been generally well tolerated in adult participants with imipenem-nonsusceptible gram-negative infections (cUTI, cIAI, or HABP/VABP). AE data from the 2 Phase 2 studies (PN003 and PN004) have demonstrated that coinfusion of IMI 500 mg and REL 250 mg q6h from 4 to 14 days has been generally well tolerated in adult participants with cUTI and cIAI, respectively, with a safety profile similar to that of IMI alone. Phase 1 studies evaluated REL as single doses up to 1150 mg, multiple doses up to 625 mg q6h for 7 days, or multiple doses up to 500 mg q6h for 14 days; no dose-limiting toxicity was observed over this range of doses up to a maximum of 14 days of dosing in a total of 59 adult participants who received REL at or above the proposed marketed dose of 250 mg (up to 625 mg REL) coinfused with 500 mg IMI for >4 days.

Dose interval and study design considerations for participants with HABP/VABP, cIAI, and cUTI are discussed in Section 4.3.3.1, Section 4.3.3.2, and Section 4.3.3.3, respectively.

4.3.3.1 Hospital-Acquired and Ventilator-Associated Bacterial Pneumonia (HABP/VABP)

For participants with HABP/VABP, IV study intervention will be administered for a minimum of 7 days up to a maximum of 14 days. Participants with evidence of concurrent bacteremia or with *P. aeruginosa* infection should receive 14 days of antibacterial treatment. Extension of study intervention beyond 14 days must be approved by the Sponsor as described in Section 4.3.3.

American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines recommend treatment of HABP/VABP for as few as 7 days, provided that the patient has a good clinical response and the infection is not caused by *P. aeruginosa* [Niederman, M. S. 2005]. If deemed clinically appropriate, participants may receive up to 14 days of study intervention for non-Pseudomonas infections. In the setting of Pseudomonas infection, a treatment duration of 14 days is predicated on data from several studies and meta-analyses, which show a lesser incidence of persistence or recurrence with ~2 weeks versus ~1 week of therapy [Pugh, R., et al 2011] [Chastre, J., et al 2003]. Lower responses and higher mortality were also recently seen following treatment with a shorter course of therapy (1 week of doripenem) versus a longer course of therapy (10 days of IMI) in *P. aeruginosa* VABP cases [Kollef, M. H., et al 2012]. An antibacterial treatment duration of 14 days for concurrent bacteremia is supported by current IDSA guidelines on the treatment of bloodstream infections and by standard clinical practice.

Further details of definitive treatment of nosocomial pneumonia in pediatric patients can be found in [Bradley, J. S. 2002]. These recommendations are similar to those for treatment of adults with HABP/VABP as suggested by the ATS/IDSA [Niederman, M. S. 2005].

4.3.3.2 Complicated Intra-Abdominal Infection (cIAI)

In general, cIAIs require a surgical procedure and parenteral antibacterial therapy. Current recommendations are to limit the antibacterial course to 4 to 7 days in cases where adequate source control has been achieved [Solomkin, J. S., et al 2010] [Skrupky, L. P., et al 2013]. In an effort to evaluate the efficacy in this study, the total duration of all study intervention for cIAI has been set at a minimum of 5 days (IV alone or IV then oral, of which at least 3 days must be IV alone before optional oral switch) up to a maximum of 14 days (IV alone or IV then oral). The investigator, based on the participant's clinical condition, may decide to switch the participant to oral antibacterial therapy after at least 3 days of IV study intervention; participants with cIAI who switch to oral therapy will have a total duration of all study antibacterial therapy (IV then oral) of a minimum of 5 days up to a maximum of 14 days. Extension of study intervention beyond 14 days must be approved by the Sponsor as described in Section 4.3.3.

Discussion of empiric treatment options for cIAI in adult and pediatric patients can be found in [Solomkin, J. S., et al 2010].

4.3.3.3 Complicated Urinary Tract Infection (cUTI)

Based on American Academy of Pediatrics treatment guidelines, the total duration of treatment for cUTIs may vary from 7 days for a lower urinary tract infection to 10 to 14 days for acute pyelonephritis [Finnell, S. M., et al 2011]. In this study, participants with cUTI will have a total duration of all study antibacterial therapy of a minimum of 5 days (IV alone or IV then oral, of which at least 3 days must be IV alone before optional oral switch) up to a maximum of 14 days (IV alone or IV then oral). The investigator, based on the participant's clinical condition, may decide to switch the participant to oral antibacterial therapy after at least 3 days of IV study intervention; participants with cUTI who switch to oral therapy will have a total duration of all study antibacterial therapy (IV then oral) of a minimum of 5 days

up to a maximum of 14 days. Extension of study intervention beyond 14 days must be approved by the Sponsor as described in Section 4.3.3.

In general, cUTIs requiring parenteral therapy are routinely treated with a short course of IV antibacterial therapy followed by oral antibacterial therapy. This switch facilitates step-down antibacterial therapy in anticipation of eventual hospital discharge. See Section 2.2.4.1 on the rationale for the optional oral switch for participants with cIAI or cUTI in this study.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent/assent. The overall study ends when the last participant completes the last study-related contact, withdraws consent/assent, or is lost to follow-up (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped as described in Appendix 1.10.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Require hospitalization and treatment with IV antibacterial therapy for confirmed or suspected gram-negative bacterial infection (in the absence of meningitis), and is expected to require hospitalization through completion of IV study intervention, with at least 1 of the following primary infection types, based on the specific criteria required to be met for the respective infection type in Appendix 8: Disease Definitions and Diagnostic Criteria:
   - Hospital-acquired bacterial pneumonia (HABP) or ventilator-associated bacterial pneumonia (VABP) (see Appendix 8 - Section 10.8.1)
   - Complicated intra-abdominal infection (cIAI) (see Appendix 8 - Section 10.8.2)
   - Complicated urinary tract infection (cUTI) (see Appendix 8 - Section 10.8.3)

NOTE: Participants less than 3 months of age can be enrolled after ruling out meningitis per Exclusion #2.

Demographics

2. Participant is male or female and is from birth to less than 18 years of age inclusive, at the time of providing documented informed consent/assent. For Age Cohorts 4 and 5, participant is at least 37 weeks postmenstrual age at the time of providing documented informed consent/assent. Postmenstrual age is calculated by adding the gestational age at the time of birth to the chronological age at the time of providing documented informed consent/assent.

Female Participants

3. Not be pregnant (Appendix 5) or breastfeeding, and at least 1 of the following conditions applies:
   a. Not be a woman of childbearing potential (WOCBP) as defined in Appendix 5.

OR

b. A WOCBP must agree to follow the contraceptive guidance in Appendix 5 during the intervention period and for at least 24 hours after the last dose of study intervention.

Informed Consent/Assent

4. The participant (or legally acceptable representative if applicable) has provided documented informed consent/assent for the study.

Additional Categories

5. Have sufficient intravascular access to receive study intervention through an existing peripheral or central line.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant meets any of the following criteria:

Medical Conditions

1. Is expected to survive less than 72 hours
2. Has a concurrent infection that would interfere with evaluation of response to the study antibacterials (IMI/REL or Active Control), including any of the following:
   - Endocarditis
   - Osteomyelitis
   - Meningitis (Participants less than 3 months of age must have documentation that meningitis has been ruled out prior to initiation of IV study intervention, in accordance with the labeled use of imipenem and cilastatin [PRIMAXIN® (US) [U.S. Prescribing Information 2017] or TIENAM® (ex-US) [Summary of Product Characteristics 2011]], which is not indicated in pediatric patients with CNS infections.)
   - Prosthetic joint infection
   - Active pulmonary tuberculosis
   - A disseminated fungal infection
   - A concomitant infection at the time of randomization that requires nonstudy systemic antibacterial therapy in addition to IV study intervention or oral step-down therapy (medications with only gram-positive activity [eg, vancomycin, linezolid] are allowed).
3. Has HABP/VABP caused by an obstructive process, including lung cancer (or other malignancy metastatic to the lungs resulting in pulmonary obstruction) or other known obstruction.

4. Has a cUTI that meets any of the following:
    - Complete obstruction of any portion of the urinary tract (ie, requiring a permanent indwelling urinary catheter or instrumentation)
    - Documented reflux of ileal loop urinary diversion
    - Suspected or confirmed perinephric or intrarenal abscess
    - Suspected or confirmed prostatitis, urethritis, or epididymitis
    - Trauma to pelvis/urinary tract
    - Presence of indwelling urinary catheter which cannot be removed at study entry

NOTE: All indwelling urinary catheters must be removed prior to the start of IV study intervention. Unless medically necessary, it is recommended that an indwelling urinary catheter not be reinserted while on IV study intervention.

5. Has any of the following medical conditions at screening:
    - A history of a seizure disorder (requiring ongoing treatment with anticonvulsive therapy or prior treatment with anticonvulsive therapy within the last 3 years)
    - Cystic fibrosis

6. Has a history of serious allergy, hypersensitivity (eg, anaphylaxis), or any serious reaction to IMI or to any of the following:
    - Any carbapenem, cephalosporin, penicillin, or other β-lactam agent
    - Other BLIs (eg, tazobactam, sulbactam, clavulanic acid, avibactam)

7. Has a history or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might expose the participant to risk by participating in the study, confound the results of the study, or interfere with the participant's participation for the full duration of the study.

Prior/Concomitant Therapy

8. If less than 3 months of age, has received more than 72 hours of empiric antibacterial treatment for suspected meningitis prior to initiation of IV study intervention.
9. If 3 months of age or older, or <3 months without suspected meningitis, has received potentially therapeutic antibacterial therapy (eg, with gram-negative activity), including bladder infusions with topical urinary antiseptics or antibacterial agents, for a duration of more than 24 hours during the 48 hours preceding the first dose of study intervention.

    NOTE: For all Age Cohorts, provided all other eligibility criteria are met, the following participants may be enrolled:

    - A participant failing prior antibiotic therapy for a current episode of cUTI or HABP/VABP who:
        a. Has received the prior antibacterial treatment for at least 48 hours

b. Has persistent clinical or radiographic findings clearly indicating ongoing infection
c. Fulfills other laboratory or microbiology criteria for enrollment

However, participants with cUTI whose final culture result does not meet the CFU/mL criteria defined in Appendix 8 - Section 10.8.3 must discontinue study intervention following the negative culture result.

- A participant failing prior antibiotic therapy for a current episode of cIAI who:
  a. Has received the prior antibacterial treatment for at least 48 hours
  b. Has persistent clinical or radiographic findings clearly indicating ongoing infection
  c. Fulfills other laboratory or microbiology criteria for enrollment
  d. Has planned operative intervention no more than 24 hours after first dose of study treatment
  e. Has not received any further nonstudy antibiotics postoperatively

10. Is anticipated to be treated with any of the following medications:
    - Valproic acid or divalproex sodium (or has used valproic acid or divalproex sodium in the 2 weeks prior to screening) through 24 hours after completion of the final dose of IV study intervention for participants who receive IMI/REL or carbapenem.
    - Concomitant IV, oral, or inhaled antimicrobial agents with gram-negative activity, in addition to those designated in the study intervention groups, during the course of all (IV/oral) study intervention.

      NOTE: Use of IV vancomycin, IV daptomycin, or IV linezolid to treat confirmed or suspected MRSA infection, use of IV linezolid or IV daptomycin to treat confirmed or suspected vancomycin-resistant Enterococcus spp. (VRE) infection, or use of trimethoprim-sulfamethoxazole (TMP/SMX) or other standard-of-care agent for prophylaxis of opportunistic infection (eg, *Pneumocystis jiroveci* infection) in immunocompromised participants is allowed. Daptomycin is not indicated for the treatment of HABP/VABP.

    - Planned receipt of suppressive/prophylactic antibiotics with gram-negative activity after completion of study intervention.

      NOTE: Based on site-level standard of care, participants at increased risk of recurrent pyelonephritis or cUTI (eg, vesico-ureteral reflux Grade 3 through 5) where there is a clear benefit to low-dose antibiotic prophylaxis may be enrolled.

Prior/Concurrent Clinical Study Experience

11. Is currently participating in or has participated in an interventional clinical study with an investigational compound or device within 30 days prior to screening.

12. Has enrolled previously in the current study and been discontinued, or has received REL for any other reason.

Diagnostic Assessments

13. Has an estimated CrCl (based on the Cockcroft-Gault equation, for participants ≥12 years of age) or estimated glomerular filtration rate (eGFR, based on the modified Schwartz equation, for participants <12 years of age) below that specified for the appropriate age range in Table 16; or requires peritoneal dialysis, hemodialysis, or hemofiltration.
14. Has alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥5 x upper limit of normal (ULN) at the time of screening.

    NOTE: Patients with acute hepatic failure or acute decompensation of chronic hepatic failure should also be excluded.

Other Exclusions

15. Is, based on medical history at the time of providing documented informed consent/assent, a user of recreational or illicit drugs or has had a recent history (within the last year) of drug or alcohol abuse or dependence.
16. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

No restrictions are required; participants will be hospitalized.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention or withdraws from the study will not be replaced.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies [study interventions provided by the Sponsor] will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 1 and organized by infection type in Table 2.

Acceptable control options for treatment of each respective infection type in the Active Control arm and acceptable oral switch options for step-down treatment of cIAI or cUTI in both intervention arms (IMI/REL and Active Control) are:

- HABP/VABP: IV carbapenem, or IV PIP/TAZ, or IV cefepime
- cIAI: IV carbapenem or IV third-generation cephalosporin + metronidazole, IV PIP/TAZ with optional oral switch to PO β-lactam/β-lactamase inhibitor combination, or PO second- or third-generation cephalosporin in combination with metronidazole, or PO quinolone (if ciprofloxacin or levofloxacin, use in combination with metronidazole)
- cUTI: IV third- or fourth-generation cephalosporin, IV ciprofloxacin, or IV meropenem with optional switch to PO β-lactam/β-lactamase inhibitor combination, or PO cephalosporin, or PO quinolone, or PO nitrofurantoin, or PO trimethoprim or trimethoprim/sulfamethoxazole

Protocol-allowed comparator medications for each infection type are detailed by generic drug name in the EDC system, EDC guidelines, and Appendix 9. The option to switch a participant with cIAI or cUTI to oral therapy after the indicated minimum number of days of IV study intervention is at the investigator's discretion based on the participant's clinical condition and local standard of care. The choice of oral switch therapy should be guided by culture results and based on local antibiotic susceptibility patterns.

IMI/REL administered by age-based dose and infusion duration is summarized in Table 3; Active Control and oral switch administered per authorized PI, SPC, or international treatment guidelines. The total duration of all study intervention must be a minimum of 5 days (cIAI and cUTI, IV alone or IV then oral, of which at least 3 days must be IV alone before optional oral switch) or 7 days (HABP/VABP, IV alone). The total duration of all study intervention for any infection type must not exceed 14 days (IV alone or IV then oral). Extension of study therapy beyond 14 days requires Sponsor approval (Section 4.3.3).

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
IMI/ REL	Experimental	IMI/REL	Drug	Powder, For Suspension	relebactam, imipenem, cilastatin 250/500/500 mg	Age Cohort 1: 500/250 mg q6h Age Cohort 2: 15/7.5 mg/kg q6h Age Cohort 3: 15/7.5 mg/kg q6h Age Cohort 4: 15/7.5 mg/kg q**6**h Age Cohort 5: 15/7.5 mg/kg q**8**h All administered as 60-minute infusions	IV Infusion	cIAI and cUTI: Total duration of all study intervention: Minimum 5 days (IV alone or IV then oral, of which at least 3 days must be IV alone before optional oral switch) up to a maximum of 14 days; HABP/VABP: Minimum 7 days up to a maximum of 14 days.	Test Product	IMP	Sponsor

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Active Control	Active Comparator	Acceptable control options for each infection type	Drug	Powder, For Suspension	Per authorized PI, SPC, or international treatment guidelines	Per authorized PI, SPC, or international treatment guidelines	IV Infusion	cIAI and cUTI: Total duration of all study intervention: Minimum 5 days (IV alone or IV then oral, of which at least 3 days must be IV alone before optional oral switch) up to a maximum of 14 days; HABP/ VABP: Minimum 7 days up to a maximum of 14 days. All administered per authorized PI, SPC, or international treatment guidelines.	Comparator	IMP	Locally

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
IMI/ REL	Experimental	Acceptable oral switch options for cIAI and cUTI	Drug	Liquid	Per authorized PI, SPC, or international treatment guidelines	Per authorized PI, SPC, or international treatment guidelines	Oral	Per authorized PI, SPC, or international treatment guidelines	Systemically Prescribed	IMP	Locally
Active Control	Active Comparator	Acceptable oral switch options for cIAI and cUTI	Drug	Liquid	Per authorized PI, SPC, or international treatment guidelines	Per authorized PI, SPC, or international treatment guidelines	Oral	Per authorized PI, SPC, or international treatment guidelines	Systemically Prescribed	IMP	Locally

cIAI=complicated intra-abdominal infection; cUTI=complicated urinary tract infection; EDC=electronic data collection; EEA=European Economic Area; HABP/VABP=hospital-acquired or ventilator-associated bacterial pneumonia; IMI/REL= imipenem/cilastatin/relebactam (MK-7655A); IMP=investigational medicinal product; IV=intravenous; NIMP/AxMP=noninvestigational/auxiliary medicinal product; PI=Package Insert; PO=per os (by mouth); q6h=every 6 hours; q8h=every 8 hours; SPC=Summary of Product Characteristics.

Note: The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

Note: Protocol-allowed comparator medications for each infection type are detailed by generic drug name in the EDC system, EDC guidelines, and Appendix 9.

Note: Study intervention, dose, and regimen are listed by infection type in Table 2.

All supplies indicated in Table 1 will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.8 for details regarding administration of the study intervention.

Table 2 Intervention, Dose, and Regimen by Infection Type

Intervention Group Name	Drug[a,b]	Dose Strength	Dose Frequency	Route of Administration[a]	Regimen/Treatment Period[a]	Use
HABP/VABP						
IMI/REL	IMI/REL	Age-based (Table 3, Section 6.1.1)	C1, C2, C3: 60-minute infusion q6h C4: 60-minute infusion q6h C5: 60-minute infusion q8h	IV	Minimum 7 days up to a maximum of 14 days	Test product
Active control	Acceptable control options for treatment of HABP/VABP are: IV carbapenem or IV PIP/TAZ or IV cefepime	Per authorized PI, SPC, or international treatment guidelines	Per authorized PI, SPC, or international treatment guidelines	IV	Minimum 7 days up to a maximum of 14 days	Standard of care
cIAI						
IMI/REL	IMI/REL with optional oral switch to:[a] PO β-lactam/β-lactamase inhibitor combination or PO second- or third-generation cephalosporin in combination with metronidazole or PO quinolone (if ciprofloxacin or levofloxacin, use in combination with metronidazole)	Age-based (Table 3, Section 6.1.1)	C1, C2, C3: 60-minute infusion q6h C4: 60-minute infusion q6h C5: 60-minute infusion q8h	IV or IV then oral	Total duration of all study interventions must be a minimum of 5 days (IV alone or IV then oral, of which at least 3 days must be IV before optional oral switch) up to a maximum of 14 days (IV alone or IV then oral)	Test product

Intervention Group Name	Drug[a,b]	Dose Strength	Dose Frequency	Route of Administration[a]	Regimen/Treatment Period[a]	Use
Active control	Acceptable control options for treatment of cIAI are: IV carbapenem or IV PIP/TAZ or IV third-generation cephalosporin + metronidazole with optional oral switch to:[a] PO β-lactam/β-lactamase inhibitor combination or PO second- or third-generation cephalosporin in combination with metronidazole or PO quinolone (if ciprofloxacin or levofloxacin, use in combination with metronidazole)	Per authorized PI, SPC, or international treatment guidelines	Per authorized PI, SPC, or international treatment guidelines	IV or IV then oral	Total duration of all study interventions must be a minimum of 5 days (IV alone or IV then oral, of which at least 3 days must be IV before optional oral switch) up to a maximum of 14 days (IV alone or IV then oral)	Standard of care
cUTI						
IMI/REL	IMI/REL with optional oral switch to:[a] PO β-lactam/β-lactamase inhibitor combination or PO cephalosporin or PO quinolone or PO nitrofurantoin or PO trimethoprim or trimethoprim/sulfamethoxazole	Age-based (Table 3, Section 6.1.1)	C1, C2, C3: 60-minute infusion q6h C4: 60-minute infusion q6h C5: 60-minute infusion q8h	IV or IV then oral	Total duration of all study interventions must be a minimum of 5 days (IV alone or IV then oral, of which at least 3 days must be IV before optional oral switch) up to a maximum of 14 days (IV alone or IV then oral)	Test product

Intervention Group Name	Drug[a,b]	Dose Strength	Dose Frequency	Route of Administration[a]	Regimen/Treatment Period[a]	Use
Active control	Acceptable control options for treatment of cUTI are: IV third- or fourth-generation cephalosporin, IV ciprofloxacin, or IV meropenem with optional oral switch to:[a] PO β-lactam/β-lactamase inhibitor combination or PO cephalosporin or PO quinolone or PO nitrofurantoin or PO trimethoprim or trimethoprim/sulfamethoxazole	Per authorized PI, SPC, or international treatment guidelines	Per authorized PI, SPC, or international treatment guidelines	IV or IV then oral	Total duration of all study interventions must be a minimum of 5 days (IV alone or IV then oral, of which at least 3 days must be IV before optional oral switch) up to a maximum of 14 days (IV alone or IV then oral)	Standard of care

C=cohort; cIAI=complicated intra-abdominal infection; cUTI=complicated urinary tract infection; EDC= electronic data collection; HABP/VABP=hospital-acquired or ventilator-associated bacterial pneumonia; IMI/REL=imipenem/cilastatin/relebactam (MK-7655A); IV=intravenous; PIP/TAZ=piperacillin/tazobactam; PI=Package Insert; PO=per os (by mouth); q6h=every 6 hours; q8h=every 8 hours; SPC=Summary of Product Characteristics.

[a] In both intervention arms (IMI/REL and Active Control), participants with cIAI or cUTI may have an optional switch to a specified oral antibacterial therapy after the indicated minimum number of days of IV study intervention at the investigator's discretion based on the participant's clinical condition and local standard of care. The choice of oral switch therapy should be guided by culture results and based on local antibiotic susceptibility patterns.

[b] Protocol-allowed comparator medications for each infection type are detailed by generic drug name in the EDC system, EDC guidelines, and Appendix 9.

6.1.1 Dose by Age Cohort

Table 3 IMI/REL Dose by Age Cohort

Age Cohort	Age Range	IMI/REL Dose[a]
1	12 to <18 years	500/250 mg q6h
2	6 to <12 years	15/7.5 mg/kg q6h
3	2 to <6 years	15/7.5 mg/kg q6h
4	3 months to <2 years	15/7.5 mg/kg q6h[b]
5	Birth to <3 months	15/7.5 mg/kg q8h[b]

FDC=fixed-dose combination; IMI/REL=imipenem/cilastatin/relebactam (MK-7655A); PK=pharmacokinetics; q6h=every 6 hours; q8h=every 8 hours.

[a] Doses for all age cohorts will be administered as 60-minute infusions and will not exceed the adult maximum single dose of IMI/REL 500 mg/250 mg. IMI/REL is provided as a single-vial FDC; therefore, the dose for each component will be adjusted proportionally during preparation.

[b] Initial doses of IMI/REL and infusion duration for participants in Age Cohorts 4 and 5 were selected based on results from the single-dose safety and PK study in pediatric participants from birth to less than 18 years of age with proven or suspected gram-negative infections (MK-7655A-020) and confirmed based on review of safety, tolerability, efficacy, and PK data from Age Cohorts 1 through 3 in the current study (PN021). Initial doses and infusion duration for Age Cohorts 4 and 5 were communicated to investigators and sites via a protocol amendment prior to initiation of enrollment of Age Cohorts 4 and 5.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Specific calculations or evaluations required to be performed to administer the proper dose to each participant are outlined in a separate document provided by the Sponsor. The rationale for selection of doses to be used in this study is provided in Section 4.3.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard

and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention allocation/randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 3:1 ratio to IMI/REL or active control, respectively.

6.3.2 Stratification

Intervention allocation/randomization will be stratified according to the following factors:

1. Age: 5 pediatric age cohorts will be evaluated in the study as follows:
   - Age Cohort 1: Adolescents (12 to <18 years)
   - Age Cohort 2: Older Children (6 to <12 years)
   - Age Cohort 3: Younger Children (2 to <6 years)
   - Age Cohort 4: Infants and Toddlers (3 months to <2 years)
   - Age Cohort 5: Neonates and Young Infants (birth to <3 months)

2. Infection Type: 3 infection types will be evaluated in the study as follows:
   - HABP/VABP
   - cIAI
   - cUTI

The IRT system will be used to limit enrollment in the study and in specific age cohorts by infection type as described in Section 4.1.

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the intervention administered.

6.4 Study Intervention Compliance

Extensions of any study intervention (IV or oral) of >14 days of therapy and interruptions from the protocol-specified study therapy plan of (1) ≥2 doses of IV study intervention during the first 3 days of therapy, OR (2) ≥4 doses of IV study intervention from Day 4 to the end of IV study intervention, OR (3) ≥4 doses of oral study intervention from the end of IV study intervention to the EOT visit all require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

Medications specifically prohibited in the exclusion criteria are not allowed during study intervention (IV or oral; see Section 5.2). If there is a clinical indication for any medication specifically prohibited during the study, discontinuation from study intervention (IV or oral) may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention (IV or oral) requires the mutual agreement of the investigator, the Sponsor, and the participant.

Listed below are specific restrictions for concomitant therapy during the course of the study:

1. Within 2 weeks prior to screening through 24 hours after completion of the final dose of IV study intervention: valproic acid or divalproex sodium.
2. During the course of all study intervention (IV alone or IV then oral): concomitant IV, oral, or inhaled antimicrobial agents with gram-negative activity, in addition to those designated in the study intervention groups.

   NOTE: Use of IV vancomycin, IV daptomycin, or IV linezolid to treat confirmed or suspected MRSA infection, use of IV linezolid or IV daptomycin to treat confirmed or suspected VRE infection, or use of TMP/SMX or other standard of care agent for prophylaxis of opportunistic infection (eg, *Pneumocystis jiroveci* infection) in immunocompromised participants is allowed. Daptomycin is not indicated for the treatment of HABP/VABP.

3. Planned receipt of suppressive/prophylactic antibiotics with gram-negative activity after completion of study intervention.

   NOTE: Based on site-level standard of care, participants at increased risk of recurrent pyelonephritis or cUTI (eg, vesico-ureteral reflux Grade 3 through 5) where there is a clear benefit to low-dose antibiotic prophylaxis may be enrolled.

   NOTE: Any licensed COVID-19 vaccine (including for emergency use) in a particular country is allowed in the study if it is an mRNA vaccine, replication-incompetent adenoviral vaccine, or inactivated vaccine. These vaccines will be treated just as any other concomitant therapy.

Investigational vaccines (ie, those not licensed or approved for emergency use) are not allowed.

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified to be used in this study.

6.6 Dose Modification (Escalation/Titration/Other)

The goal of this study is to determine the safety, tolerability, efficacy, and PK profile of IMI/REL for each pediatric age cohort at doses that achieve an acceptable safety, tolerability, and efficacy profile and similar exposure as that seen in clinical studies in adults and pediatric participants. Based on available data from PN020, dose modification for Cohorts 1, 2, and 3 from those specified in Table 3 is not anticipated in this study.

As noted in Table 3, the initial doses of IMI/REL and infusion duration for participants in Age Cohorts 4 and 5 were selected based on results from PN020 and confirmed based on review of safety, tolerability, efficacy, and PK data from Age Cohorts 1, 2, and 3 in this study (PN021). Initial doses for Age Cohorts 4 and 5 are in Section 6.1.1.

If unexpected PK results require dose modification for any age cohort(s) during the study, a protocol amendment will be developed.

6.7 Intervention After the End of the Study

There is no study-specified intervention following the end of the study.

6.8 Clinical Supplies Disclosure

This study is open label; therefore, the participant, the study site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text.

6.9 Standard Policies

Not applicable, as this study uses active controls.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to be monitored in the study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.10.3 unless the participant has withdrawn from the study (Section 7.2).

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study intervention, but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant has a medical condition or personal circumstance, which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- The participant has HABP/VABP and the infection-site specimen Gram stain shows the presence of gram-positive cocci **only**.
- The participant has cUTI, but does not have a positive urine culture result that meets the cUTI Microbiological criteria in Appendix 8 - Section 10.8.3.
- The participant has estimated CrCl (based on the Cockcroft-Gault equation) or eGFR (based on the modified Schwartz equation) below the normal level specified for the appropriate age range in Table 16; or requires peritoneal dialysis, hemodialysis, or hemofiltration.

For participants who are discontinued from study intervention, but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

Discontinuation from study intervention is permanent. Once a participant is discontinued, the participant shall not be allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a prescreening log to record details of all participants prescreened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent/assent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

It is recognized that pediatric centers reduce required blood volumes for standard clinical testing based on the size of the child, with many centers suggesting a 0.5 mL blood draw for most standard clinical tests in neonates (eg, blood culture, hematology with differential, and clinical chemistry panels). With this in mind, expected blood volumes for the youngest participants (neonates) are calculated in Table 4.

Table 4 Approximate Blood Volumes Drawn in Neonates by Study Visit, Sample Type

Study Visit:	Screening Visit[a]	Intervention Visits				Follow-up Visits		Overall Total
		Day 1[a]	OTX	EOIV[b,c]	EOT[c]	EFU[d]	LFU[d]	
Blood Parameter	**Approximate Blood Volume (mL)**							
Hematology	0.5			0.5		0.5		
Blood Chemistry	0.5			0.5		0.5		
Blood Culture		As clinically indicated						
Plasma Pharmacokinetics		0.75 (3×250 µL)	0.25 (1×250 µL)					
Expected Total	**1.75**		**0.25**	**1**		**1**		**4**

cIAI=complicated intra-abdominal infection; cUTI=complicated urinary tract infection; EFU=early follow-up; EOIV=end of IV therapy; EOT=end of therapy; LFU=late follow-up; OTX=on therapy; SoA=schedule of activities.
Note: Clinically significant abnormal results must be repeated until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

[a] For screening, the most recent local laboratory results available ≤48 hr prior to randomization may be used (repeat testing not needed on Day 1).

[b] Only for participants with cIAI or cUTI who switch to oral therapy (see the SoA).

[c] Blood collection for Hematology and Blood Chemistry must be performed at: (1) the EOIV visit for participants with cIAI or cUTI who switch to oral therapy, OR (2) the EOT visit for participants with cIAI or cUTI who do not switch to oral therapy and for all participants with HABP/VABP.

[d] Blood collection for Hematology and Blood Chemistry must be performed within 14 days after EOT at either the EFU visit or LFU visit.

The approximate total blood volume to be drawn is within 3% of total blood volume (2.4 mL blood per kg of body weight) even for the lowest approximate weight for eligible participants in this study (ie, female neonates in the fifth percentile of growth according to World Health Organization growth charts). The maximum amount of blood collected from each participant over the duration of the study will not exceed 3% of total blood volume (2.4 mL blood per kg of body weight).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent/Assent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent and assent, if applicable, from each potential participant (or their legally acceptable representative) prior to participating in this clinical study. If there are changes to the participant's status during the study (eg, health or age of

majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent/assent is in place.

8.1.1.1 General Informed Consent/Assent

Informed consent/assent given by the participant or their legally acceptable representative must be documented on a consent/assent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent/assent discussion.

A copy of the signed and dated informed consent/assent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial informed consent/assent form, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent/assent form or addendum to the original consent/assent form that captures the participant's or the participant's legally acceptable representative's dated signature.

Specifics about the study and the study population are to be included in the study informed consent/assent form.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements. The assent, as applicable, will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent/assent. At the time of intervention allocation/randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant ID card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. In addition to the evaluation of a participant's medical history in terms of study eligibility, all medical conditions present during the 12 months prior to study entry will be documented at the screening visit on the appropriate electronic case report form (eCRF).

Any history of prior HABP or VABP, cIAI, or cUTI episodes or conditions that may predispose a participant to the development of a pulmonary, abdominal, or urinary tract infection, respectively, will also be documented on the appropriate eCRF, even if the prior episode or predisposing condition was diagnosed more than 12 months prior to study entry.

The details of any primary (HABP/VABP, cIAI, cUTI) or secondary bacterial infection-site diagnoses will be documented separately on the appropriate eCRF(s). Details should include the diagnosis and any additional diagnostic details associated with the infection site (eg, characterization of the complicated nature of the cIAI and/or cUTI).

For participants less than 3 months of age (Cohort 5), details specific to neonates and young infants, including details of the meningitis evaluation and assessment of absence of meningitis, will also be documented on the appropriate eCRF.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 14 days and any antimicrobial medication taken within 30 days prior to the first dose of IV study intervention. For breastfed participants, medications taken by the mother during the same timeframe will also be recorded. See Section 5.2 on prior antibacterial therapy.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study. For breastfed participants, medications taken by the mother during the study will also be recorded.

See Section 5.2 for excluded medications and Section 6.5 on concomitant therapy during study intervention (IV or oral).

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any individual who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening/rescreening visit requirements are provided in Section 8.10.1. Pretrial screening logs may be collected for review by the Sponsor. If applicable, any information that would make the participant identifiable will be removed.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a randomization number. The randomization number identifies the participant for all procedures occurring after randomization. Once a randomization number is assigned to a participant, it can never be reassigned to another participant.

A single participant cannot be assigned more than 1 randomization number.

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or appropriately qualified designee according to the specifications within the pharmacy manual and will be recorded in the appropriate eCRF.

Study intervention should begin on the day of randomization or as close as possible to the date on which the participant is assigned.

8.1.8.1 Timing of Dose Administration

8.1.8.1.1 IV Study Intervention

The frequency of IMI/REL (Intervention Group 1) IV administration will be q6h or q8h as shown in Table 3. Each infusion should be administered within 60 minutes of the scheduled dose. IMI/REL should be administered over the duration appropriate for the age cohort as shown in Table 3.

The frequency and duration of Active Control (Intervention Group 2) IV administration will be per the authorized PI, SPC, or international treatment guidelines.

The study intervention must NOT be administered simultaneously through the same infusion line/lumen with any other drugs (including other IV study or IV nonstudy interventions). If another IV drug is required either prior to or after study intervention and only 1 line/lumen is available, an appropriate volume of saline flush must be used between IV infusions. In instances when IMI/REL or Active Control require administration at the same hour of the day as any other drugs (including other IV study or IV nonstudy interventions), the 2 infusions should be administered either 1) sequentially with the IMI/REL infusion first followed by an appropriate volume of saline flush prior to administration of the other IV drug; OR 2) via a separate infusion line at the same time as the other IV drug.

Additional details for preparation and administration of study intervention are provided in the pharmacy manual. For participants randomized to receive IMI/REL, sites will contact the

IRT to request additional doses beyond the initial supply provided for the minimum treatment duration, as needed during the study IV intervention period, as indicated in the SoA.

8.1.8.1.2 Optional Oral Switch (cIAI, cUTI)

For participants with cIAI or cUTI, the investigator may decide to switch the participant to oral antibacterial therapy, to facilitate step-down in anticipation of discharge, based on the participant's clinical condition and local standard of care. The list of acceptable oral switch options is provided in Table 1 and Appendix 9. IV study intervention is intended to be administered to participants with cIAI or cUTI for a minimum of 3 full days as in Table 1, after which participants with cIAI or cUTI in either intervention arm (IMI/REL or Active Control) who have demonstrated adequate response to IV study intervention may be switched to oral antibacterial therapy. The frequency of oral administration will be per the authorized PI, SPC, or international treatment guidelines (Table 1). Some participants with cIAI or cUTI may have limited reliable oral options for treatment of their infections and may still require IV study intervention to complete the entire duration of antibacterial treatment.

The decision to switch to oral therapy must be based on investigator assessment of the participant's clinical signs and symptoms related to local and systemic improvement, as follows:

1. The participant has received at least 3 full days of IV study intervention, as in Table 1;
2. The participant has been afebrile for at least 24 hours, defined as having a maximal daily body temperature <38.0°C (100.4°F) and without the influence of aspirin, acetaminophen (paracetamol), or nonsteroidal anti-inflammatory drugs; if the participant is taking analgesic medication with antipyretic activity, temperature readings (to determine clinical response) should be determined at the end of the analgesic dosing interval.
3. Nausea or vomiting, if present prestudy, has resolved, and improvement is noted in the following (if present prestudy) without evidence of worsening:
   a. Flank pain/CVA tenderness, as assessed by severity scoring (none, mild, moderate, or severe); AND
   b. Leukocytosis

   In determining the switch to oral antibacterial therapy, the additional clinical signs and symptoms of cIAI or cUTI listed in Table 5 may also be considered.
4. For participants with cUTI, at least 1 follow-up urine culture has shown eradication of the uropathogen (Table 8 and Table 9). All participants with cUTI must have a repeat urine culture obtained after completion of at least 3 days of IV study intervention (ie, prior to the oral switch) to assess whether suppression/eradication of admission uropathogens has occurred (repeat catheterization not required).

These findings will be documented on the appropriate eCRFs for each of these participants.

See also Section 8.2.2.1 on cIAI and cUTI clinical signs and symptoms and Section 9.11 on oral therapy compliance.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.10.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.10 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study.

8.1.11 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy Assessments

Definition of the efficacy endpoints and a summary of favorable response by efficacy endpoint and analysis population are provided in Table 11.

8.2.1 All-cause Mortality (28-day Survival Assessment)

For each participant, 28-day survival status (ie, whether the participant is alive or dead at Day 28 post-randomization) will be collected. Results of the assessment, including date and cause of death if relevant, will be recorded on the appropriate eCRF at the EFU or LFU visit or telephone call, as specified in the SoA. In addition to the Day 28 post-randomization survival assessment, all deaths that occur during the study period will be reported as part of routine safety assessment.

8.2.2 Clinical Response

8.2.2.1 Clinical Signs and Symptoms Review

A detailed diagnosis as well as relevant clinical information associated with diagnosis, including clinical signs and symptoms, relevant radiographic, and laboratory characteristics related to the primary and any secondary bacterial infections sites, will be reviewed and documented on the appropriate eCRFs at the time points specified in the SoA.

Presence or absence of specific clinical signs and symptoms for each infection type (Table 5) will be recorded daily during IV study intervention and at the visits specified in the SoA. Intensity of signs and symptoms will also be graded by the investigator as mild, moderate, or severe as described in Appendix 3.

Clinical signs and symptoms for each infection type, including those listed in Table 5 and in Appendix 8, will be monitored by the Primary Investigator (or designee) at baseline and throughout the study to determine resolution, persistence, or progression at each time point specified in the SoA, Table 6, and Table 7.

Table 5 Clinical Signs and Symptoms for Each Infection Type

Infection Type	Clinical Signs and Symptoms[a]	
HABP/VABP	New onset or worsening of cough, dyspnea, tachypnea (eg, respiratory rate greater than 25 breaths per minute), expectorated sputum production, requirement for mechanical ventilation, hypoxemia, need for acute changes in the ventilator support system to enhance oxygenation, as determined by worsening oxygenation (via ABG or PaO_2/FiO_2 assessment), needed changes in the amount of positive end-expiratory pressure, new onset of suctioned respiratory secretions, fever or hypothermia, chills/rigors, chest pain	
cIAI	Fever or hypothermia, hypotension, abdominal pain, flank pain, pain caused by cIAI that is referred to another anatomic area such as back or hip, tenderness to palpation, rebound tenderness, guarding, mass, nausea and vomiting, anorexia, altered mental status	
cUTI	If 0 to <2 years of age: - Fever - Failure to thrive - Recent weight loss - Irritability - Poor feeding - Lack of normal level of activity - Abdominal pain/tenderness on physical examination - Vomiting - Jaundice	If 2 to <18 years of age: - Fever - Chills or rigors - Dysuria - Urinary urgency Urinary frequency New-onset urinary incontinence - Suprapubic pain, flank pain, abdominal pain, or pelvic pain - Suprapubic tenderness or CVA tenderness on physical examination - Nausea or vomiting

ABG=arterial blood gas; cIAI=complicated intra-abdominal infection; cUTI=complicated urinary tract infection; CVA=costovertebral angle; HABP/VABP=hospital-acquired or ventilator-associated bacterial pneumonia; PaO_2/FiO_2=partial pressure of oxygen to the fraction of inspired oxygen.

[a] Evaluation of clinical response for infection type may also include resolution of laboratory abnormalities present at baseline (see Appendix 8 for relevant laboratory abnormalities for each infection type).

8.2.2.2 Investigator Rating and Sponsor Categorization of Clinical Response

The investigator will determine and record the clinical response rating at each visit (per the SoA) as described in Table 6 and Table 7 based on comparison to baseline clinical signs and symptoms of the participant's infection.

The Sponsor will use this rating to categorize the clinical response as "favorable" or "unfavorable".

Table 6 Clinical Response Ratings at the EOIV and EOT Visits

Clinical Response[a]	**Response Definition**
Cure	All preintervention signs and symptoms[b] of the index infection have resolved (or returned to “preinfection status", with no new symptoms) **AND** no additional antibacterial intervention is required for the index infection.
Improved	The majority of preintervention signs and symptoms[b] of the index infection have improved or resolved (or returned to “preinfection status", with no new symptoms) **AND** no additional antibacterial intervention is required.
Failure	No apparent response to study intervention in prestudy signs and symptoms[b] of the index infection: persistence or progression of the majority of or all preintervention signs and symptoms.
Indeterminate	Study data are not available for evaluation of clinical response for any reason at the visit, including: Complication related to underlying medical condition; **OR** Participant was withdrawn for any reason before sufficient data had been obtained to permit evaluation for any reason; **OR** Extenuating circumstances (eg, an important protocol deviation) preclude classification as "cure," "improved," or "failure;" **OR** Death occurred during the study period and the index infection was clearly noncontributory.

EOIV=end of IV therapy; EOT=end of therapy.

[a] A favorable clinical response at EOT requires an assessment of “cure” or “improved”.

[b] Refer to Section 8.2.2.1 and Table 5 for a description of relevant clinical signs and symptoms.

Table 7 Clinical Response Ratings at the EFU and LFU Visits

Clinical Response[a]	**Response Definition**
Sustained Cure	All preintervention signs and symptoms[b] of the index infection have resolved (or returned to "preinfection status", with no new symptoms) with no evidence of resurgence **AND** no additional antibacterial intervention is required for the index infection.
Cure	All preintervention signs and symptoms[b] of the index infection have resolved (or returned to “preinfection status", with no new symptoms) **AND** no additional antibacterial intervention is required for the index infection.
Failure	No apparent response or insufficient response to study intervention in prestudy signs and symptoms of the index infection: persistence, progression, or improvement (without full resolution) of all preintervention signs and symptoms.[b]
Relapse	Participants with a favorable clinical response (cure or improvement) at the EOT visit have new or worsening signs and symptoms[b] of the index infection by the EFU or LFU visit.

Clinical Response[a]	Response Definition
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: a) Complication related to underlying medical condition; **OR** b) Participant was withdrawn for any reason before sufficient data had been obtained to permit evaluation of clinical response; **OR** c) Extenuating circumstances (eg, an important protocol deviation) preclude classification as "sustained cure," "failure," or "relapse;" **OR** d) Death occurred during the study period and the index infection was clearly noncontributory.

EFU=early follow-up; EOT=end of therapy; LFU=late follow-up.

[a] A favorable clinical response at EFU or LFU requires an assessment of “cure” or “sustained cure”. To be considered “sustained cure”, the clinical response for the prior visit (EOT or EFU) must have been considered “cure”.

[b] Refer to Section 8.2.2.1 and Table 5 for a description of clinical signs and symptoms.

8.2.3 Microbiological Response

As described in Section 4.2.2.1.3, microbiological response will be evaluated separately for each baseline pathogen meeting the culture criteria in Section 8.2.3.1 (ie, by-pathogen).

The investigator will determine the by-pathogen microbiological response rating at the visits specified in the SoA based on local laboratory results of available infection-site and blood cultures collected relative to the pathogen(s) isolated at baseline, as detailed in Section 8.2.3.2.

8.2.3.1 Infection Site and Blood Specimens for Gram Stain, Culture, and Susceptibility Testing

The requirements for collection of infection-site specimens for culture and susceptibility testing for participants with HABP/VABP, cIAI, and cUTI are outlined in Section 8.2.3.1.1, Section 8.2.3.1.2, and Section 8.2.3.1.3, respectively. Gram stain is only required for participants with HABP/VABP (see Section 8.2.3.1.1). The requirements for collection of blood samples for culture and susceptibility testing are outlined in Section 8.2.3.1.4.

Infection site and blood specimens should be processed by the local laboratory for Gram stain (HABP/VABP only), culture, and susceptibility testing according to recognized methods for each specimen/infection type. All organisms isolated from culture that are considered to be etiologic pathogens by the investigator will be retained by the local clinical microbiology laboratory and sent to the central microbiology laboratory as instructed in the microbiology laboratory manual. Suspected causative bacterial pathogens should also be stored at the local laboratory for possible future testing, if needed.

In addition to testing by the central microbiology laboratory, culture (aerobic and anaerobic) and in vitro susceptibility testing may be performed for medical management by the site’s local laboratory per each laboratory’s standard procedures. Relevant culture data, including

date of collection, specimen type (including method of collection), and pathogen identification (to the species level, if identified) must be collected on the appropriate eCRFs.

8.2.3.1.1 HABP/VABP: Lower Respiratory Tract Specimen(s) for Gram Stain, Culture, and Susceptibility Testing

Baseline Lower Respiratory Tract Specimen

Participants with HABP/VABP will have a baseline (at or within 48 hours of the screening visit) LRT sample obtained, as medically acceptable, from the infection site for Gram stain, culture, and susceptibility testing prior to initiation of IV study intervention as specified in the SoA and Appendix 8 – Section 10.8.1.

Microscopic examination of Gram-stained smears must be performed for LRT specimens collected prior to randomization to ensure the adequacy/quality of the specimen and to discontinue participants with only gram-positive cocci detected (Section 7.1). For specimens obtained by direct sampling of the LRT (ie, via BAL, mini-BAL, or protected brush specimen [PBS]), no predefined requirements are required to ascertain the quality of the respiratory specimen. However, for baseline specimens not obtained by direct sampling of the LRT, such as those obtained by expectorated sputum, the low-power microscopic view of the Gram stain can be used to ascertain the quality of the respiratory specimen. This helps to ensure that the respiratory specimen sent for culture does not represent oropharyngeal contamination (eg, fewer than 10 squamous epithelial cells and greater than 25 neutrophils is an example of an adequate expectorated/suctioned sputum specimen). In addition, a high-power microscopic view of the Gram stain can be used to characterize the general type of bacteria causing the pneumonia. Specimens should be processed for culture according to recognized methods.

Post-baseline Lower Respiratory Tract Specimen (If Clinically Indicated)

Participants with HABP/VABP who have an LRT sample collected from the infection site post-baseline (post-randomization), if clinically indicated, will also have culture and susceptibility testing of any identified pathogens.

Post-baseline LRT cultures would preferentially include samples collected from a tracheostomy or endotracheal aspirates, or bronchoscopy specimens. Expectorated or induced sputum samples are also accepted provided the sample does not represent oropharyngeal contamination (ie, sample contains fewer than 10 squamous epithelial cells on low-power microscopy review of the Gram stain).

LRT samples may also be collected if there is clinical or laboratory evidence of persistence or progression of the infectious process (including persistent fever, elevated WBC count, or significant changes in the participant's clinical condition). Of note, specimens should also be collected at any time of surgical or drainage procedure (if required).

8.2.3.1.2 cIAI: Intra-abdominal Specimen(s) for Culture and Susceptibility Testing

Baseline Intra-abdominal Specimen

Participants with cIAI will have a baseline intra-abdominal specimen collected at or within 48 hours of the screening visit (intra- or post-operatively) or within 24 hours of randomization (preoperative), as medically acceptable, from purulent material from an intra-abdominal surgical procedure or percutaneous drainage from the infection site for culture (of aerobic and anaerobic organisms) and susceptibility testing prior to initiation of IV study intervention as specified in the SoA and Appendix 8 - Section 10.8.2.

Specimens should be collected at the beginning of the surgical procedure prior to debridement, removal, or disinfection of the primary site of infection. Aspirates (collected with a needle or syringe) or needle biopsy samples are recommended, and swabs of purulent material are discouraged. Specimens should not be obtained from in situ abdominal drains. Specimens should not be taken from the gallbladder bile, gallbladder wall, or from bile in the common bile duct.

Post-baseline Intra-abdominal Specimen(s) (If Clinically Indicated)

Post-baseline (post-randomization) intra-abdominal specimens for culture and susceptibility testing are to be obtained from the site of infection if clinically indicated (eg, if reintervention is required, collection during the additional surgical procedure in participants with cIAI who have clinical failure) to evaluate the microbiological assessment. Specimens should not be obtained from in situ abdominal drains. All culture and susceptibility testing of any post-baseline specimens should be performed as for the baseline sample.

8.2.3.1.3 cUTI: Urine Specimens for Culture and Susceptibility Testing

Baseline Urine Specimen

Participants with cUTI will have a baseline (at or within 48 hours of screening) urine specimen collected prior to the start of IV study intervention, preferably obtained prior to administration of any potentially therapeutic antibacterials. Testing will be performed on all organisms considered to be pathogens (quantification of uropathogens is required) in urine specimens obtained by MSCC, straight catheter, indwelling urethral catheter, or SPA (urine samples obtained from collection bags are not allowed for the study-qualifying baseline urine culture specimen), as specified in the SoA and Appendix 8 - Section 10.8.3.

Post-baseline Urine Specimens

Post-baseline (post-randomization) urine specimens will be collected for culture and susceptibility testing at the time points indicated in the SoA from participants able to provide a clean urine specimen as for the baseline urine specimen.

The use of sterile urine collection bags is allowed for young children who are unable to provide MSCC or other urine specimens at post-baseline visits. However, urine microscopy must be performed to detect pyuria in the urine sample; if pyuria is not present (as defined in

Appendix 8 - Section 10.8.3), then bacterial growth other than the uropathogen at study entry may be considered a contaminant rather than a true superinfection or new infection.

8.2.3.1.4 Blood Specimen(s) for Culture and Susceptibility Testing

Baseline Blood Sample

As clinically indicated, participants will have a blood sample collected at baseline (screening) for blood culture and susceptibility testing.

Postbaseline Blood Sample(s) (If Positive Baseline Culture And As Clinically Indicated)

Participants with positive baseline blood cultures should have follow-up blood cultures collected until a subsequent follow-up culture demonstrates no growth. Follow-up blood cultures in participants with no evidence of bacteremia (ie, positive blood cultures) at study entry should also be performed as clinically indicated, at the investigator's discretion.

8.2.3.2 Investigator Rating and Sponsor Categorization of Microbiological Response

Microbiological response will be determined for each pathogen for participants with infection-site cultures available (see Section 8.2.3.1). For a bacterial organism to be considered a pathogen at admission, it must be a typical lung, abdominal, or urinary pathogen (ie, not a normal colonizer or contaminant).

The investigator will determine a by-pathogen microbiological response rating for the respective infection type at the EOIV (for participants with cIAI or cUTI who switch to oral therapy) and EOT visits (Table 8) and at the EFU and LFU visits (Table 9). This rating will be based on the local laboratory results of infection-site cultures (Section 8.2.3.1) collected for participants at each of these visits (when available) relative to the pathogen(s) isolated at baseline.

The Sponsor will use the by-pathogen microbiological response rating determined by the investigator at each of the EOIV (for participants with cIAI or cUTI who switch to oral therapy), EOT, EFU, and LFU visits to categorize the overall microbiological response (ie, overall microbiological response for the participant based on the response of all pathogens present in the baseline culture) as "favorable" or "unfavorable".

For participants from whom only 1 pathogen is isolated in the baseline infection-site culture, the microbiological response assessment will be based on the microbiological response rating for that pathogen. For participants from whom more than 1 baseline pathogen is isolated in the baseline infection-site culture, the microbiological response outcome will be based on microbiological culture results for all pathogens (ie, a "favorable" overall microbiological response requires eradication or presumed eradication of all baseline pathogens).

Table 8 By-Pathogen Microbiological Response Ratings at the EOIV and EOT Visits

Microbiological Response[a,b,c]	**Response Definition**
Eradication	HABP/VABP: A lower respiratory tract culture taken at the EOT visit[c] shows eradication of the pathogen found at study entry. cIAI: An intra-abdominal culture taken at the EOIV or EOT visit[c] shows eradication of the pathogen found at study entry. cUTI: A urine culture taken at the EOIV or EOT visit[c] shows eradication of the uropathogen (reduced to $<10^3$ CFU/mL) found at study entry.
Presumed Eradication	No specimen taken because participant is deemed clinically improved or cured of the pathogen found at study entry.
Persistence[d]	HABP/VABP: A lower respiratory tract culture taken at the EOT visit[c] grows the pathogen found at study entry. cIAI: An intra-abdominal culture taken at the EOIV or EOT visit[c] grows the pathogen found at study entry. cUTI: A urine culture taken at the EOIV or EOT visit[c] grows the uropathogen (at $\geq 10^3$ CFU/mL) found at study entry.
Superinfection[e]	HABP/VABP: A lower respiratory tract culture taken at the EOT visit[c] grows a pathogen other than a baseline pathogen during the course of IV study intervention **OR** emergence during IV study intervention of a new pathogen at a distant sterile site along with new or worsening signs and symptoms of infection. cIAI: An intra-abdominal culture taken at the EOIV or EOT visit[c] grows a pathogen other than a baseline pathogen during the course of IV study intervention **OR** emergence during IV study intervention of a new pathogen at a distant sterile site along with new or worsening signs and symptoms of infection. cUTI: A urine culture taken at the EOIV or EOT visit[c] grows a uropathogen (at $\geq 10^5$ CFU/mL) other than a baseline pathogen during the course of IV study intervention **OR** emergence during IV study intervention of a new pathogen at a distant sterile site along with new or worsening signs and symptoms of infection.
Indeterminate	Follow-up culture is not available at the EOIV or EOT visit[c] due to participant death or withdrawal from study; **OR** Available microbiological data are incomplete (eg, sample collected, but no results available); **OR** Extenuating circumstances (eg, an important protocol deviation) preclude microbiological assessment; **OR** Any other circumstance which makes it impossible to define the microbiological response.

CFU=colony-forming unit; cIAI=complicated intra-abdominal infection; cUTI=complicated urinary tract infection; EOIV=end of IV therapy; EOT=end of therapy; HABP/VABP=hospital-acquired or ventilator-associated bacterial pneumonia; IV=intravenous.

[a] A microbiological response rating must be completed separately for each pathogen isolated at study entry. If a new/emergent pathogen is identified at this visit, which was not identified at baseline, the microbiological response rating should be recorded as "superinfection" for any new/emergent pathogen isolated after initiation of IV study therapy.

[b] A favorable by-pathogen microbiological response at EOT requires "eradication" or "presumed eradication" of the pathogen found at study entry.

[c] If a culture is not available at EOT, an assessment at this visit can be made from the last available culture collected after at least 72 hours of IV study intervention. If a culture is not available at EOT for cIAI or cUTI participants who receive oral switch, an assessment at this visit can be made from the last available culture collected after at least 48 hours of oral study intervention.

[d] If a participant is discontinued from IV or oral study intervention due to clinical failure (ie, unfavorable clinical response), but persistence of the admission pathogen is not confirmed by culture results or no culture is obtained at the time of clinical failure, the admission pathogen will be presumed to have persisted.

[e] For cUTI, if sterile urine collection bag method is used for post-baseline sampling, see Section 8.2.3.1.3.

Table 9 By-pathogen Microbiological Response Ratings at the EFU and LFU Visits

Microbiological Response[a,b,c]	**Response Definition**
Eradication	HABP/VABP: A lower respiratory tract culture taken at the EFU or LFU[c] visit shows eradication of the pathogen found at study entry. cIAI: An intra-abdominal culture taken at the EFU or LFU visit[c] shows eradication of the pathogen found at study entry. cUTI: A urine culture taken at the EFU or LFU visit[c] shows eradication of the uropathogen (reduced to <103 CFU/mL) found at study entry.
Presumed Eradication	No specimen taken because participant is deemed clinically improved or cured of the pathogen found at study entry.
Persistence	HABP/VABP: A lower respiratory tract culture taken at the EFU or LFU visit grows the pathogen found at study entry. cIAI: An intra-abdominal culture taken at the EFU or LFU visit[c] grows the pathogen found at study entry. cUTI: A urine culture taken at the EFU or LFU visit[c] grows the uropathogen (at ≥103 CFU/mL) found at study entry.
New Infection[d]	HABP/VABP: A pathogen other than an original microorganism found at study entry is present in the lower respiratory tract culture any time after completion of IV or oral study intervention; **OR** A pathogen is isolated from a distant sterile site after completion of IV or oral study intervention. cIAI: A pathogen other than an original microorganism found at study entry is present in the intra-abdominal culture any time after completion of IV or oral study intervention; **OR** A pathogen is isolated from a distant sterile site after completion of IV or oral study intervention. cUTI: A urine culture grows a uropathogen (at ≥105 CFU/mL) other than a baseline pathogen during the course of IV study intervention, **OR** emergence during IV study intervention of a new pathogen at a distant sterile site along with new and/or worsening signs and symptoms of infection.
Recurrence[d]	HABP/VABP: A lower respiratory tract culture grows the baseline pathogen taken any time after documented eradication. cIAI: An intra-abdominal culture grows the baseline pathogen taken any time after documented eradication. cUTI: A urine culture grows the baseline uropathogen (at ≥105 CFU/mL) taken any time after documented eradication.
Indeterminate	a) Follow-up culture is not available at the EFU or LFU visit due to participant death or withdrawal from study; **OR** b) Available microbiological data are incomplete (eg, sample collected, but no results available); **OR** c) Extenuating circumstances (eg, an important protocol deviation) preclude microbiological assessment; **OR** d) Any other circumstance which makes it impossible to define the microbiological response.

Microbiological Response[a,b,c]	Response Definition
CFU=colony-forming unit; cIAI=complicated intra-abdominal infection; cUTI=complicated urinary tract infection; EFU=early follow-up; EOT=end of therapy; HABP/VABP=hospital-acquired or ventilator-associated bacterial pneumonia; IV=intravenous; LFU=late follow-up.	
[a] A microbiological response rating must be completed separately for each pathogen isolated at study entry. If a new/emergent pathogen is identified at this visit, which was not identified at study entry, the microbiological response rating should be recorded as "new infection" for any new/emergent pathogen isolated after initiation of IV study intervention.	
[b] A favorable by-pathogen microbiological response at the EFU or LFU visit requires "eradication" or "presumed eradication" of the pathogen found at study entry.	
[c] If a culture is not available at EFU or LFU, an assessment at this visit can be made based on the culture collected at EOT as long as it was collected at least 24 hours after the completion of IV or oral study intervention and before the EFU or LFU visit and provided the participant had fully resolved clinical symptoms/signs of the index infection at the EFU or LFU visit.	
[d] For cUTI, if sterile urine collection bag method is used for post-baseline sampling, see Section 8.2.3.1.3.	

8.2.4 By-pathogen Microbiological Response

Microbiological response will also be evaluated separately for each baseline pathogen and the Sponsor will categorize individual by-pathogen microbiological response for participants with post-baseline infection-site culture(s) as favorable or unfavorable based on the individual pathogen rating determined by the investigator, as described in Section 8.2.3.2.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood volumes drawn by visit and by sample type per participant, can be found in Section 8.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Full and Directed Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard.

A complete physical examination, performed at randomization includes the following assessments: general appearance, head, eyes, ears/nose/ throat, neck, lymph nodes, skin, lungs, heart, abdomen, musculoskeletal, and neurologic evaluations. Breast, rectal, and genitourinary/pelvic exams should be performed when clinically indicated. After the initial full physical examination, brief directed physical examinations targeted to the participant's illness, condition, and complaints will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard at the visits indicated in the SoA. The directed physical examination should note any changes in the participant's condition (body systems) since the last examination and does not preclude examination of any of the body systems as clinically indicated.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Any abnormal or clinically significant findings from the physical examinations must be recorded on the appropriate eCRF. If observed prior to initiation of IV study therapy, changes in physical examination findings (abnormalities) that the investigator considers clinically significant will be recorded on the medical history eCRF. If observed after initiation of IV study intervention (including during oral therapy), changes in physical examination findings (abnormalities) that the investigator considers clinically significant must be recorded as AEs (see Section 8.4.1).

8.3.2 Height and Weight

An investigator or medically qualified designee (consistent with local requirements) as per institutional standard will measure and record the participant's height (cm) and weight (kg) at the visits indicated in the SoA. Weight will be measured without shoes, jacket, or diaper (for participants using diapers). A bed scale may be used if needed for participants who cannot sit up for any reason (eg, infants, intubated participants).

If applicable, any weight change that occurs during IV study intervention that may result in discontinuation (based on the estimated CrCl or eGFR value per Section 7.1 and Table 16) must be reported to the IRT as indicated in the SoA (IRT Contact) as well as recorded on the appropriate eCRF.

8.3.3 Vital Signs

- The following will be assessed by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard as indicated in the SoA:
  - Temperature: Oral or rectal temperatures should be taken as appropriate for the participant's clinical condition and age; if not possible, then tympanic or axillary methods are acceptable. Temperature readings should be taken at approximately the same time each day.
  - Systolic and diastolic blood pressure
  - Heart rate
  - Respiratory rate
- Blood pressure and heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Vital signs will be measured before blood collection for laboratory tests with the participants in a seated or semisupine position or, for participants who cannot sit up for any reason (eg, infants, intubated participants), in a supine or semisupine position, after 10 minutes rest.

Any abnormal or clinically significant findings from the vital sign measurements must be recorded on the appropriate eCRF.

8.3.4 Meningitis Evaluation

As required in Section 5.2 exclusion criterion #2 for participants <3 months of age, the investigator must rule out meningitis and document its absence prior to initiation of IV study intervention. The investigator may rule out meningitis by performing an LP with CSF culture (if clinically indicated per local standard-of-care) or by other standard-of-care procedures or clinical assessments. Negative results from a previous procedure or assessment may be used to document that meningitis has been ruled out for such participants provided these results are available at the time of screening. Investigator assessment of the absence of meningitis must be recorded on the appropriate source documents.

8.3.5 Adverse Event Monitoring

8.3.5.1 Clinical Adverse Events

Clinical AEs will be collected from the time of initiation of the first dose of IV study therapy through 14 days following completion of all study therapy. All AEs should be documented on the appropriate eCRF.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered AEs. Examples of this may include, but are not limited to, teething, typical crying in infants and children, and onset of menses or menopause occurring at a physiologically appropriate time.

See Section 8.4 for details regarding assessment and documentation of AEs.

8.3.5.2 Local Infusion Site Tolerability

Local infusion site tolerability will be evaluated daily during IV study therapy. The tolerability of all study therapy at the local IV infusion site will be based on investigator inspection and participant comments regarding signs and symptoms of intolerance. The IV infusion site should be observed daily during IV therapy to determine the presence/absence of erythema, induration, pain, tenderness, warmth, swelling, ulceration, local phlebitis, rash, or other reactions.

8.3.5.3 Laboratory Adverse Experiences

Laboratory adverse experiences will be based on safety laboratory tests (both central and local results), including hematology and chemistry tests from blood and urinalysis from urine. See the SoA on the timing of sample collection and Section 8.3.7 and Appendix 2 for the types of laboratory tests to be performed.

8.3.5.4 Adverse Events Leading to Death

All deaths that occur during the study period will be reported as part of routine safety assessment, as described.

8.3.6 Clinical Signs and Symptoms of Infection

A detailed diagnosis and relevant clinical information associated with diagnosis including clinical signs and symptoms, radiographic, and laboratory characteristics (see Appendix 2) related to the primary (HABP/VABP, cIAI, cUTI) and any secondary bacterial infections sites will be reviewed by the investigator and documented on the appropriate eCRFs at the time points specified in the SoA.

Presence or absence of specific clinical signs and symptoms relevant for the infection site of interest will be reviewed by the investigator and recorded daily during IV study intervention and at the visits specified in the SoA. Intensity of signs and symptoms will also be graded by the investigator as mild, moderate, or severe as described in Appendix 3.

8.3.6.1 Infection Source Control Review

Information related to infection source control must be collected for all participants at the visits specified in the SoA. The following information specific to the site(s) of bacterial infection must be collected for participants with:

- HABP/VABP: (a) details regarding intubation, extubation, reintubation, or replacement of the endotracheal tube, (b) details regarding lung procedures/surgeries performed to drain/remove a loculated pulmonary infection; and (c) details regarding a thoracentesis procedure to drain any accompanying pleural fluid;
- cIAI: details associated with the qualifying abdominal surgical intervention or any subsequent interventions, including an anonymized narrative of the operative note and/or interventional radiology report; or
- cUTI: baseline information associated with catheterization (eg, recent surgical procedure or instrumentation, presence of catheter/stent) as well as any details related to removal and/or replacement of urinary catheters at any time during the study.

Relevant information regarding infection source control should be documented on the appropriate eCRF.

8.3.6.2 O2 Saturation (HABP/VABP Only)

In participants with HABP/VABP, oxygen (O2) saturation via pulse oximetry will be collected on Day 1 prior to the initiation of IV study intervention, then daily until completion of IV study intervention, as well as at the EOT, EFU, and LFU visits. All measured values should be documented on the appropriate eCRF.

If available, as clinically indicated, in ventilated participants with HABP/VABP who have an existing arterial line, PaO2 and FiO2 measured via ABG should also be recorded on the appropriate eCRF.

8.3.6.3 Chest X-ray

In participants with HABP/VABP, a baseline chest x-ray must be performed as required in Appendix 8 - Section 10.8.1 and indicated in the SoA. For randomization, a chest x-ray is not required if a prior chest x-ray or chest CT has been performed in association with the current infection within 48 hours of randomization.

Post-baseline (including at EOT and, if applicable, at the discontinuation visit), chest x-ray is only to be performed if clinically indicated.

Chest x-ray results (or prior chest CT results, if relevant) including a description, location, and extent of infiltrates or consolidation must be documented on the appropriate eCRF. The presence of a pleural effusion and other abnormalities should also be noted.

8.3.7 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity, and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent/assent, but before intervention allocation/randomization, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment; if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

From the time of intervention allocation/randomization through 14 days after cessation of treatment, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside the period specified in the previous paragraph must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 10.

Table 10 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Period: Consent to Randomization/ Allocation**	**Reporting Period: Randomization/ Allocation Through Protocol-specified Follow-up Period**	**Reporting Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor**
NSAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Report if: – drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: – participant has been exposed to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in) – causes exclusion Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – potential DILI – require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

Type of Event	**Reporting Period: Consent to Randomization/ Allocation**	**Reporting Period: Randomization/ Allocation Through Protocol-specified Follow-up Period**	**Reporting Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor**
Cancer	Report if: – due to intervention – causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: – receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding (spontaneously reported to the investigator or their designee) that occurs in a participant during the study is reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing that the fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus. Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.4.7 Events of Clinical Interest

Selected serious and nonserious AEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
   *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

2. A confirmed (ie, verified by repeat testing) elevated AST or ALT laboratory value that is greater than or equal to 5× ULN as a result of within-protocol-specific testing or unscheduled testing.

8.5 Treatment of Overdose

In this study, an overdose is any dose higher than 10% of the calculated age-appropriate dose specified in Section 6.1.1 – Dose by Age Cohort (Table 3) or in subsequent protocol clarification letters.

No specific information is available on the treatment of overdose.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

The decision as to which plasma samples collected will be assayed for evaluation of PK/pharmacodynamics will be collaboratively determined by the Sponsor. If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for additional pharmacodynamic markers.

8.6.1 Blood Collection for Plasma Relebactam, Imipenem, and Cilastatin

Sample collection, storage, and shipment instructions for plasma samples will be provided in the operations/laboratory manual. All PK samples must be drawn within the specified time windows, and the actual sampling times must be documented.

The method of collection for PK samples is at the discretion of the investigator (eg, peripherally inserted central catheter line, indwelling catheter access, individual peripheral phlebotomies, peri-operatively placed arterial line). A separate IV line for PK sample collection is highly recommended; if a separate IV line is not clinically feasible, refer to the operations/laboratory manual for further details of allowable alternative collection methods.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Future Biomedical Research Sample Collection

Future biomedical research samples will not be collected in this study.

8.9 Planned Genetic Analysis Sample Collection

Planned genetic analysis samples will not be evaluated in this study.

8.10 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.10.1 Screening

Approximately 2 days prior to intervention randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Screening procedures may be repeated after consultation with the Sponsor. If the participant is rescreened, screening procedures should be repeated, unless they fall within the window specified.

8.10.2 Intervention Period

Details regarding procedures, assessments, and scheduling windows for the Day 1 (Randomization), OTX, EOIV (only for participants who switch to oral therapy), and EOT visits (ie, Visits 2, 3, 4, and 5) are presented in the SoA; notably, for participants who receive IMI/REL, blood samples for plasma PK assessments and vital sign measurements will be collected several times at Visit 2 and, for participants who switch to oral therapy, the OTX and EOIV visits (Visits 2 and 3) may be combined if both occur on Day 3.

8.10.3 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

Participants who discontinue treatment (eg, participants who discontinue from IV study intervention partway through the infusion or who discontinue from oral study intervention) or who withdraw from the study at any point after the initiation of IV study intervention will continue to be monitored in the study. These participants should have all safety assessments, including clinical safety laboratory assessments, vital sign measurements, directed physical examination, collection of AEs and concomitant medications, and local tolerability monitoring (for participants who discontinue from IV study intervention or withdraw from the study between the initiation of IV study intervention and the EOT visit) completed as per the SoA, but do not need to have PK sampling performed.

Participants who withdraw from the study prior to initiation of the first dose of study intervention (eg, due to removal of consent by the legally acceptable representative or due to an emergent condition or circumstance, which, in the opinion of the investigator or Sponsor, places the participant at unnecessary risk through continued participation, or does not allow adherence to the protocol) do not need to have further visits or assessments.

8.10.4 Poststudy

Participants will be required to return to the clinic 7 to 14 days (depending on the duration of study treatment) after completion of the last dose of all study intervention (IV or oral) for the EFU visit and again 7 to 14 days after the EFU visit for the LFU visit (ie, Visits 6 and 7). If both poststudy (EFU and LFU) visits occur prior to Day 28 post-randomization, a subsequent survival assessment telephone call should be made on Day 28 (+3 days [ie, 28 to 31 days]) post-randomization to assess the participant's 28-day survival. See the SoA for further details.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Section 9.2 to Section 9.12.

Study Design Overview	A Phase 2/3 Open-label, Randomized, Active-controlled Clinical Study to Evaluate the Safety, Tolerability, Efficacy and Pharmacokinetics of MK-7655A in Pediatric Participants From Birth to Less Than 18 Years of Age With Confirmed or Suspected Gram-negative Bacterial Infection
Treatment Assignment	Participants with HABP/VABP, cIAI, or cUTI will be randomized in a 3:1 ratio to receive IMI/REL or active control. Randomized participants will be stratified by age cohort and infection type. Five pediatric age cohorts will be evaluated in the study: • Age Cohort 1: Adolescents (12 to <18 years) • Age Cohort 2: Older Children (6 to <12 years) • Age Cohort 3: Younger Children (2 to <6 years) • Age Cohort 4: Infants and Toddlers (3 months to <2 years) • Age Cohort 5: Neonates and Young Infants (birth to <3 months) Three infection types will be evaluated in the study: • HABP/VABP • cIAI • cUTI
Analysis Populations	**Safety:** All Participants as Treated (APaT) **Efficacy:** Modified intent-to-treat (MITT) and microbiological MITT (mMITT) **Pharmacokinetics:** Pharmacokinetic (PK)
Primary Endpoint(s)	**Safety endpoints:** • Adverse events (AEs) • IV study intervention discontinuations due to AEs
Key Secondary Endpoints	**Efficacy endpoints:** • All-cause mortality • Favorable clinical response • Favorable microbiological response **Pharmacokinetic endpoints:** • Plasma concentrations of imipenem and relebactam (REL) • $AUC_{0\text{-}24hr}$ and C_{eoi} for imipenem and REL • %T>MIC for imipenem

Statistical Methods for Key Efficacy/ Pharmacokinetic Analyses	**Efficacy analysis:** Within-group 95% confidence intervals for the efficacy endpoints will be calculated using the Agresti & Coull method. Point estimates and between-group 95% confidence intervals for efficacy endpoints will be calculated using unstratified Miettinen and Nurminen method. There will be no efficacy hypothesis testing conducted in this estimation study. **Pharmacokinetic analysis:** The pediatric population PK model developed using adult and PN020 pediatric PK data will be updated with PN021 PK data and used to calculate the PK endpoints.
Statistical Methods for Key Safety Analyses	The tiers differ with respect to the analyses that will be performed. There are no Tier 1 events. For Tier 2 events, point estimates and 95% CIs will be provided for between-treatment differences in the percentage of participants with events and these analyses will be performed using the Miettinen and Nurminen method. For Tier 3 safety parameters, only point estimates by intervention group will be provided. The analysis of safety results will be performed for overall participants. In addition, the analysis for some Tier 2 endpoints will be performed for each age cohort and for each infection type separately.
Interim Analyses	A review of safety and tolerability data will be conducted by an independent external Data Monitoring Committee (eDMC) in this study when Age Cohorts 2 and 3 have achieved at least 20 participants each with complete data available (all complete data available from Age Cohorts 1, 2, and 3 will be reviewed at this time), along with periodic reviews as described in the DMC charter. No formal efficacy analyses will be conducted for eDMC review; however, protocol-specific summary statistics for PK data and/or key efficacy endpoints can be provided to the eDMC on request to support benefit-to-risk evaluation. An internal interim review of subgroup analyses of safety, tolerability, efficacy, and PK data from each of Age Cohorts 1 through 3 has been performed prior to enrollment of Age Cohorts 4 and 5, with the doses communicated via Amendment 03.
Multiplicity	No multiplicity adjustment is planned.
Sample Size and Power	Approximately 140 participants will be randomized in a 3:1 ratio to receive IMI/REL or active control to target having 132 participants (approximately 99 in the IMI/REL and approximately 33 in the active control group in the safety analysis population). In each of the 5 age cohorts, the following number of participants will be randomized: • Age Cohort 1: No more than 12 participants • Age Cohorts 2 and 3: At least 20 participants in each age cohort • Age Cohorts 4 and 5: At least 28 participants in each age cohort By each of the 3 infection types, the following number of participants will be randomized: • HABP/VABP and cIAI - At least 28 participants • cIAI: At least 10% of participants with diagnosis other than complicated appendicitis • cUTI: No more than 48 participants in Age Cohorts 3, 4, and 5 combined There are no hypotheses to be evaluated, but Section 9.9 provides information about two-sided 95% confidence intervals for the proportion of participants assessed as a success under varying assumptions for the number of successes in both treatment groups.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study is being conducted as an open-label study (ie, participants, investigators, and Sponsor personnel will be aware of participant intervention assignments after each participant is enrolled and intervention is assigned).

The Sponsor will generate the randomized allocation schedule(s) for study intervention assignment.

9.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3. This is an estimation study and no formal hypothesis testing will be performed.

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below.

9.4.1 Efficacy Endpoints

A full description of efficacy assessments is contained in Section 8.2.

The efficacy endpoints of interest include:

- All-cause mortality through Day 28 post-randomization
- Favorable clinical response at the EOT, EFU, and LFU visits
- Favorable microbiological response at the EOT, EFU, and LFU visits

The exploratory efficacy endpoints include:

- Favorable clinical response at the EOIV visit (for oral switch participants)
- Favorable microbiological response at the EOIV visit (for oral switch participants)
- Favorable by-pathogen microbiological response at the EOIV (for oral switch participants), EOT, EFU, and LFU visits

The efficacy measures and assessments required to achieve a favorable response are summarized in Table 11.

Table 11 Summary of Efficacy Endpoints and Components of a Favorable Response

Objective	Endpoint	Timing	Assessment for Favorable Response	Analysis Population	References (Section/Table)
Secondary	All-Cause Mortality	Day 28	Survival	MITT	Section 8.2.1
	Favorable Clinical Response	EOT	• Cure • Improved	MITT	Section 8.2.2 Table 6
	Favorable Clinical Response	EFU, LFU	• Sustained cure • Cure	MITT	Section 8.2.2 Table 7
	Favorable Microbiological Response	EOT, EFU, LFU	• Eradication • Presumed eradication	mMITT	Section 8.2.3 Table 8 Table 9
Exploratory	Favorable Clinical Response	EOIV	• Cure • Improved	For oral switch participants in MITT	Section 8.2.2 Table 6
	Favorable Microbiological Response	EOIV	• Eradication • Presumed eradication	For oral switch participants in mMITT	Section 8.2.3 Table 8
	Favorable By-pathogen Microbiological Response	EOIV	• Eradication • Presumed eradication	For oral switch participants in mMITT	Section 8.2.3 Table 8 Section 8.2.4
	Favorable By-pathogen Microbiological Response	EOT, EFU, LFU	• Eradication • Presumed eradication	mMITT	Section 8.2.3 Table 8 Table 9 Section 8.2.4

Day 28=Day 28 post-randomization; EFU=early follow-up; EOIV=end of IV therapy; EOT=end of therapy; LFU=late follow-up; MITT=modified intent-to-treat population; mMITT=microbiological modified intent-to-treat population.

9.4.2 Safety Endpoints

A description of safety measures is contained in Sections 8.3 and 8.4. The analysis of safety results is described in Section 9.6.2.

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, local tolerability assessments, clinical laboratory evaluations, vital sign measurements and physical examinations.

The safety analysis endpoints are:

- AEs, including:
  - Any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, and an AE that resulted in death
  - A local infusion site intolerance AE (erythema, induration, pain, tenderness, warmth, swelling, ulceration, local phlebitis, rash, etc.) during IV study intervention

  - Safety laboratory AEs (based on safety laboratory test results, including hematology and chemistry tests from blood and urinalysis from urine)
- IV study intervention discontinuations due to AEs, including:
  - Discontinuation of IV study intervention due to an AE
  - Discontinuation of IV study intervention due to a drug-related AE

9.4.3 Pharmacokinetics Endpoints

The PK endpoints are:

- Plasma concentrations of imipenem and REL
- $AUC_{0\text{-}24hr}$ and C_{eoi} for imipenem and REL. $AUC_{0\text{-}24hr}$ for REL will be used to calculate fAUC$_{0\text{-}24hr}$/MIC.
- %T>MIC for imipenem

Plasma concentrations of REL, imipenem, and cilastatin will be measured. Sparse PK sampling will be performed during the IV study intervention period on all participants enrolled in the study, consisting of 3 samples per participant (30 minutes prior to start of the first dose of IV study intervention; within 10 minutes after the end of the first infusion ; and 2 to 6 hours after the start of the first IV infusion) on Day 1, plus 1 sample on 1 additional day from Day 2 to 3 at 2 to 6 hours after the start of any infusion that day. Cilastatin PK data will be collected and analyzed, but further analyses on cilastatin PK will not be performed unless required.

For REL, plasma exposure ($AUC_{0\text{-}24hr}$), fAUC$_{0\text{-}24hr}$/MIC and C_{max} will be the primary endpoints. For imipenem, % fT>MIC, plasma exposure ($AUC_{0\text{-}24hr}$), and C_{max} will be the primary endpoints. Imipenem % fT>MIC represents the percentage of the total dosing interval in which the imipenem free (adjusted for protein binding) concentration is higher than the MIC. In addition, the following population PK model-based mean PK parameters for both REL and imipenem will be determined: clearance (CL) and volume of distribution for the central compartment (Vc). All REL and imipenem endpoints and parameters will be calculated using a pediatric population PK model. In fAUC$_{0\text{-}24hr}$/MIC and % fT>MIC, f means adjusted for REL and imipenem protein binding, respectively. The population PK analysis will be summarized in a separate pediatric population PK modeling and simulation report.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The MITT and the mMITT populations will serve as the efficacy analysis populations.

For analyzing all-cause mortality through Day 28 post-randomization and clinical responses in this study, the MITT population will include randomized participants who received at least 1 dose of IV study intervention.

For analyzing microbiological responses in this study, the mMITT population will include randomized participants who meet the following conditions:

- For participants with HABP/VABP and cIAI:
  1. The participant received at least 1 dose of IV study intervention; AND
  2. The participant's baseline infection-site culture grew at least 1 gram-negative pathogenic organism.
- For participants with cUTI:
  1. The participant received at least 1 dose of IV study intervention; AND
  2. The participant's baseline urine culture grew at least 1 gram-negative pathogenic organism at sufficient quantity (ie, growth at ≥105 CFU/mL of uropathogen) as specified in the cUTI Microbiological Criteria in Appendix 8 - Section 10.8.3.

Participants will be included in the treatment group to which they were randomized for the analysis of efficacy data using both the MITT and mMITT populations. Details on the approach to handling missing data are provided in Section 9.6.2.

9.5.2 Safety Analysis Populations

Safety analyses will be conducted in the APaT population, which consists of all randomized participants who received at least 1 dose of IV study intervention. Participants will be included in the treatment group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population, which will generally be the treatment group to which the participants are randomized; however, participants who take incorrect study intervention for the entire treatment period will be included in the treatment group corresponding to the study intervention actually received.

At least 1 laboratory or vital sign measurement obtained after at least one dose of IV study intervention is required for inclusion in the analysis of the respective safety parameter.

9.5.3 Pharmacokinetics Populations

The PK population will be used for the PK analysis. This population is the subset of participants who comply with dosing and PK sampling sufficiently to ensure that these data will be likely to exhibit the anticipated PK endpoints, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements, and absence of major protocol violations. Participants with major protocol violations will be identified to the extent possible by individuals responsible for data collection/compliance and its analysis and interpretation. Any participants or data values excluded from analysis will be identified, along with their reasons for exclusion, in the pediatric population PK modeling and simulation report.

At the end of the study, all participants who are compliant with the study procedure as described and have at least 1 postdose PK data point available will be included in the PK analysis dataset.

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

This is an estimation study; no formal statistical testing will be performed for the efficacy endpoints. All of the efficacy endpoints in this study are binary. Within-group 95% confidence intervals for these endpoints will be calculated using the Agresti & Coull method [Agresti, A. and Coull, B. A. 1998]. In addition, 95% confidence intervals for between-treatment differences in the incidence (or percentage of participants) will be calculated using the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985], an unconditional, asymptotic method.

If enrollment in Age Cohorts 4 (3 months to <2 years) and 5 (birth to 3 months) is found to considerably delay completion of this study, the primary analysis will be based on Age Cohorts 1, 2, and 3 combined.

Missing values

Any participant missing an evaluation for a specific endpoint (clinical or microbiological) at any particular visit will be generally considered as being "indeterminate" for that endpoint in the MITT and mMITT populations. The following are exceptions to this rule:

- Participants discontinuing IV or oral study intervention due to lack of efficacy (ie, withdrawals with subsequent nonstudy antibacterial therapy) will be considered as "failures" with respect to clinical response at the time of discontinuation and all subsequent time points.
- Participants discontinuing IV or oral study intervention due to lack of efficacy will be presumed to have "persistence" for the microbiological response at the time of discontinuation and all subsequent time points.

The efficacy endpoints, analysis population, and statistical methods that will be used for the efficacy analyses are presented in Table 12. Since a favorable clinical response at EOIV, EOT requires an assessment of "cure" or "improved", an assessment of "indeterminate" would be considered a failure to achieve a favorable clinical response. In addition, since a favorable clinical response at EFU and LFU requires an assessment of "cure" or "sustained cure," an assessment of "indeterminate" would be considered a failure to achieve a favorable clinical response. Since a favorable microbiological response at EOIV, EOT, EFU, and LFU requires an assessment of "eradication" or "presumed eradication", an assessment of "indeterminate" would be considered a failure to achieve a favorable microbiological response.

Table 12 Analysis Strategy for Efficacy Variables

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Efficacy Endpoints			
Incidence of all-cause mortality through Day 28 post-randomization	Unstratified M&N	MITT	Missing=Failure
Proportion of participants with a favorable clinical response at the EOT, EFU, and LFU visits	Unstratified M&N	MITT	Missing=Failure
Proportion of participants with a favorable microbiological response at the EOT, EFU, and LFU visits	Unstratified M&N	mMITT	Missing=Failure
Exploratory Efficacy Endpoints			
Proportion of participants with a favorable clinical response at the EOIV visit	Descriptive Statistics	For oral switch participants in MITT	Missing=Failure
Proportion of participants with a favorable microbiological response at the EOIV visit	Descriptive Statistics	For oral switch participants in mMITT	Missing=Failure
Proportion of pathogens with a favorable by-pathogen microbiological response at the EOIV visit	Descriptive Statistics	For oral switch participants in mMITT	Missing=Failure
Proportion of pathogens with a favorable by-pathogen microbiological response at the EOT, EFU, and LFU visits	Descriptive Statistics	mMITT	Missing=Failure

Day 28=Day 28 post-randomization; EOIV=end of IV therapy; EOT=end of therapy; EFU=early follow-up; LFU=late follow-up; MITT=Modified intent-to-treat; mMITT=microbiological modified intent-to-treat; M&N=Miettinen and Nurminen method (1985).

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and laboratory tests. Safety assessment will also include close monitoring for potential hepatic toxicity and include protocol-defined ECIs related to elevated transaminase findings.

The following are considered prespecified ECIs:

1. Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3X ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2X ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2X ULN, as a result of within-protocol-specific testing or unscheduled testing.
2. A confirmed (ie, verified by repeat testing) elevated AST or ALT laboratory value that is greater than or equal to 5X ULN as a result of within-protocol-specific testing or unscheduled testing.

The analysis of safety results will follow a tiered approach (Table 13). The tiers differ with respect to the analyses that will be performed. AEs (specific terms as well as system organ class terms), protocol predefined ECIs and events that meet predefined limits of change in laboratory are either prespecified as "Tier 1" endpoints, or will be classified as belonging to "Tier 2" or "Tier 3" based on the number of events observed.

Tier 1 Events

Safety parameters or AEs of special interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance. There are no Tier 1 events for this protocol as this is an estimation study; no formal statistical testing will be performed.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for differences in the proportion of participants with events, also via the unstratified M&N method (1985).

Membership in Tier 2 requires that at least 12 participants in the experimental intervention group (Intervention Group 1 [IG1]: IMI/REL) or 2 participants in the control group (Intervention Group 2 [IG2]: Active Control) exhibit the event; all other AEs and predefined limits of change will belong to Tier 3.

The thresholds of events were chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when fewer participants per group, respectively, experience events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse events and safety parameters that meet predefined limits of change. Only targeted measurements of predefined limits of change will be summarized/analyzed as described in the sSAP.

In addition to individual events that occur in 12 or more participants in the experimental intervention group and in 2 or more participants in the control group, the broad AE categories consisting of the proportion of participants with any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, discontinuation of IV study intervention due to an AE, and discontinuation of IV study intervention due to a drug-related AE will be considered Tier 2 endpoints.

The analysis for some Tier 2 endpoints (any AE, a drug-related AE, a serious AE, a serious and drug-related AE, ECIs, discontinuation of IV study intervention due to an AE, and discontinuation of IV study intervention due to a drug-related AE) will be provided for each age cohort and for each infection type separately.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Continuous Safety Measures

No summaries of continuous measures such as changes from baseline in laboratory or vital signs are planned.

Table 13 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint[a]	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	ECI#1	X	X
	ECI#2	X	X
	Any AE[b]	X	X
	Any Serious AE	X	X
	Any Drug-Related AE	X	X
	Any Serious and Drug-Related AE	X	X
	IV study intervention discontinuation due to AE	X	X
	IV study intervention discontinuation due to Drug-Related AE	X	X
	Specific AEs[c] by SOC and PT, or PDLCs (incidence ≥12 participants in the experimental intervention group or ≥2 participants in the control group)	X	X
Tier 3	Specific AEs[c] by SOC and PT, or PDLCs[a] (incidence <12 participants in the experimental intervention group and <2 participants in the control group)		X

AE(s)=adverse event(s); ECI=event of clinical interest; IV=intravenous; PDLC=predefined limit of change; PT=Preferred Term; SOC=System Organ Class; X=results will be provided.

[a] AE refers to both clinical and laboratory AEs.

[b] Indicates broad AE category of the number of participants reporting any AE.

[c] Including local infusion site intolerance AEs during IV study intervention (erythema, induration, pain, tenderness, warmth, swelling, ulceration, local phlebitis, rash, etc.).

9.6.3 Statistical Methods for Pharmacokinetics Analysis

The sample at end of infusion will help further characterize C_{max} and the second sample during the elimination phase window will help confirm the AUC and time above MIC estimation. Relebactam and imipenem PK data will be added to existing pediatric PK data from PN020 to further update the pediatric population PK model. Any missing postdose plasma concentrations will be treated as missing. Values below the limit of quantification will be assigned a value of zero. A nonlinear mixed effects modeling approach will be used for model building.

Adult PK targets for REL and imipenem will be used. The goal of model-based simulations will be to confirm that these targets are jointly achieved in a proportion of pediatric participants similarly covered in adults (~90% probability of target attainment) for each age cohort; hence, achieving these targets implies similar efficacy as that obtained in adults. An

absolute (mg) or weight-based (mg/kg) dose, whichever is found most suitable for each age cohort, will be selected based on the simulation results.

As this is an estimation study; no formal statistical testing will be performed for the PK data. In all, the additional REL and imipenem PK data collected in this study will be used to update the population PK model and confirm adequacy of selected doses. The population PK analysis will be summarized in a pediatric population PK modeling and simulation report.

9.6.4 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by the use of summary tables. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables (eg, age, race, and gender), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

A review of safety and tolerability data will be conducted by an independent eDMC in this study when Age Cohorts 2 and 3 have each achieved at least 20 participants with complete data available (all complete data available from Age Cohorts 1, 2, and 3 will be reviewed at this time), along with periodic reviews as described in the eDMC charter. A description of the structure, function, and guidelines for decision-making by the eDMC, along with the timing and content of the safety reviews will be outlined in the eDMC charter. Information regarding the composition of the eDMC is provided in Appendix 1.

No formal efficacy analyses will be conducted for eDMC review; however, protocol-specific summary statistics for PK data and/or key efficacy endpoints can be provided to the eDMC on request to support benefit-to-risk evaluation.

Study enrollment is likely to be ongoing at the time of any interim analyses. The results of interim analyses will not be shared with the investigators prior to the completion of the study.

The eDMC will serve as the primary reviewer of the results of the interim analyses of the study and will make recommendations for discontinuation of the study or protocol modifications (including any potential dose modifications) to an executive committee of the Sponsor. Additional details are provided in the eDMC Charter.

In addition to the eDMC interim review of safety and tolerability data, an internal interim review of complete separate and aggregated safety, tolerability, efficacy, and PK data from Age Cohorts 1 through 3 will be performed prior to enrollment of Age Cohorts 4 and 5. This internal interim review will be conducted independently from the eDMC interim review, but will consider any critical safety findings in the eDMC assessment. Results will be reviewed by an internal team to assess whether the safety, tolerability, efficacy, and PK profile is acceptable for each age cohort. The findings from the internal interim review were used to confirm the proposed doses for Age Cohorts 4 and 5 (Section 6.1.1).

An interim analysis to assess safety, tolerability, efficacy, and PK may be performed when final data from Age Cohorts 1 to 3 are available.

9.8 Multiplicity

No multiplicity adjustment is planned.

9.9 Sample Size and Power Calculations

This study will randomize approximately 140 participants in a 3:1 ratio into 2 treatment groups (Intervention Group 1 [IG1]: IMI/REL and Intervention Group 2 [IG2]: active control), to obtain 132 participants (approximately 99 participants in IG1 and 33 participants in IG2) in the safety analysis population. No more than 12 participants will be randomized to Age Cohort 1; at least 20 participants will be randomized to each of Age Cohorts 2 and 3; and at least 28 participants will be randomized to each of Age Cohorts 4 and 5. At least 28 participants with HABP/VABP or cIAI will be enrolled. In addition, no more than 48 participants with cUTI may be enrolled in Age Cohorts 3, 4, and 5 combined, and a target of at least 10% of participants with cIAI should have a diagnosis other than complicated appendicitis.

As many of the safety endpoints and all of the efficacy endpoints are binary, justification of the sample size is based on the precision of these estimates as assessed by the width of the 95% within-group confidence intervals (Table 14). Displays of the two-sided 95% confidence intervals for the proportion of participants assessed as a success under varying assumptions for the number of successes in IG1 (IMI/REL) and IG2 (active control) are provided. Estimates are provided for:

- N=3 (number of IG2 participants in Age Cohort 1)
- N=9 (number of IG1 participants in Age Cohort 1)
- N=5 (number of IG2 participants in each of Age Cohorts 2 and 3)
- N=15 (number of IG1 participants in each of Age Cohorts 2 and 3)
- N=7 (number of IG2 participants in Age Cohorts 4 and 5)
- N=21 (number of IG1 participants in Age Cohorts 4 and 5)
- N=33 (number of IG2 participants combined across age cohorts)
- N=99 (number of IG1 participants combined across age cohorts)

Table 14 Two-Sided 95% Confidence Intervals

Number of Participants in Population	Observed Number With Success	(%)	Two-Sided 95% Confidence Interval (Agresti & Coull method) (%)
4	1	25%	(3.4, 71.1)
	3	75%	(28.9, 96.6)
5	2	40%	(11.6, 77.1)
	4	80%	(36.0, 98.0)
7	2	28.6%	(7.6, 64.8)
	4	57.1%	(25.0, 84.3)
	6	85.7%	(46.7, 99.5)
8	2	25%	(6.3, 59.9)
	4	50%	(21.5, 78.5)
	7	87.5%	(50.8, 99.9)
15	5	33.3%	(15.0, 58.5)
	10	66.7%	(41.5, 85.0)
	13	86.7%	(60.9, 97.5)
21	5	23.8%	(10.2, 45.5)
	10	47.6%	(28.3, 67.6)
	15	71.4%	(49.8, 86.4)
	20	95.2%	(75.6, 100)
33	7	21.2%	(10.4, 38.1)
	15	45.5%	(29.8, 62.0)
	23	69.7%	(52.5, 82.8)
	31	93.9%	(79.4, 99.3)
99	20	20.2%	(13.4, 29.2)
	45	45.5%	(36.0, 55.3)
	70	70.7%	(61.1, 78.8)
	95	96.0%	(89.7, 98.7)

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the incidence of Day 28 all-cause mortality and the proportion of participants with a favorable clinical response at EFU within each treatment group (MITT population) will be estimated within each category of the following classification variables (assessed prior to or at the point of randomization):

- Stratification variable: Age
  - Age Cohort 1: 12 to <18 years
  - Age Cohort 2: 6 to <12 years
  - Age Cohort 3: 2 to <6 years
  - Age Cohort 4: 3 months to <2 years
  - Age Cohort 5: Birth to <3 months
- Stratification variable: Baseline Infection type
  - HABP/VABP
  - cIAI

- cUTI

- Gender (female, male)
- Race (white, non-white)

Additional subgroup analysis summaries with regard to other intrinsic factors may be considered as needed.

9.11 Compliance (Medication Adherence)

This is a study in hospitalized participants in whom study medication is initially administered IV and in-hospital and is, therefore, expected to follow the protocol strictly without compliance issues. Any medication errors will be monitored and recorded.

In this study, at the discretion of the investigator, participants with cIAI or cUTI may be switched to oral antibacterial therapy after at least 3 days of IV study intervention. Participants with evidence of concurrent bacteremia or with *P. aeruginosa* infection should receive 14 days of antibacterial treatment.

As part of the routine recording of the amount of antibacterial therapy taken by each participant, study staff will record any remaining product (eg, pill count or liquid volume) following completion of oral therapy. The number of oral doses dispensed and taken will be counted, reviewed, and recorded at the EOT visit. This information will be recorded on the appropriate eCRF.

9.12 Extent of Exposure

The extent of exposure to study treatment will be evaluated by summary statistics (ie, N, mean, median, standard deviation) and/or frequencies for the "Number of Days on Therapy" by treatment group.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (eg, contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy, and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing, in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All clinical trials will be reviewed and approved by an IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and MSD will approve the participant informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or representative), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (eg, to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee, affiliated institution, and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees. Data generated by this study will be

considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules, and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 Executive Oversight Committee

The EOC is comprised of members of Sponsor Senior Management. The EOC will receive and decide on any recommendations made by the eDMC regarding the study.

10.1.4.2 External Data Monitoring Committee (eDMC)

To supplement the routine study monitoring outlined in this protocol, an eDMC will periodically monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the eDMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The eDMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the eDMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7 Interim Analyses) and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation

of eDMC reports, minutes, and recommendations will be described in the eDMC charter that is reviewed and approved by all the eDMC members.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

For investigators located in countries with serious breach reporting requirements, investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol which is likely to affect to a significant degree: (i) the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study-site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

Safety Laboratory Assessments

- The tests detailed in Table 15 will be performed by the local laboratory.
- Local laboratory results used to make either a study intervention decision or response evaluation must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 15 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes		WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Chemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose nonfasting	Calcium	Alkaline phosphatase	Carbon dioxide
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Serum or urine β-human chorionic gonadotropin (β-hCG) pregnancy test (as needed for WOCBP)			

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

10.2.1 Renal Function Ranges

Renal function below that specified in Table 16 for the appropriate age range based on estimated CrCl (using the Cockcroft-Gault equation) or eGFR (using the modified Schwartz equation) is an exclusion criterion for this study (see Section 5.2).

In addition to values obtained from scheduled chemistry blood draws during the study, the serum creatinine values used to calculate CrCl or eGFR for eligibility determination will also be recorded on the appropriate eCRF. Only those local laboratory abnormalities in serum creatinine that result in an AE or a clinically significant change in estimated CrCl or eGFR, which may or may not result in discontinuation, should be collected on the appropriate eCRF.

Participants whose renal function decreases during study medication administration to a CrCl or eGFR value below that specified for the appropriate age range (Table 16), confirmed on repeat testing, should generally be discontinued from study medication. However, investigators may discuss continuing therapy in participants with transient changes in renal function due to acute illness with the Sponsor.

Table 16 Acceptable Renal Function Ranges for Study Inclusion Based on Estimated Creatinine Clearance or Estimated Glomerular Filtration Rate by Age Range

Age Range	**Acceptable Range for Inclusion**	
	CrCl[a] (mL/min)	**eGFR[b,c] (mL/min/1.73 m^2)**
12 to <18 years	≥90	
2 to <12 years		≥90
18 months to <2 years		≥76
12 to <18 months		≥73
8 to <12 months		≥65
14 weeks to <8 months		≥57
6 to <14 weeks		≥47
2 to <6 weeks		≥41
1 to <2 weeks		≥25
Birth to <1 week		≥20

Age Range	Acceptable Range for Inclusion	
	CrCl[a] (mL/min)	**eGFR[b,c] (mL/min/1.73 m^2)**

CrCl=creatinine clearance; eGFR=estimated glomerular filtration rate.

[a] FDA guidance [Food and Drug Administration (CDER) 2014] recommends classifying renal function based on estimated creatinine clearance (CrCl, mL/min) using the modified Cockcroft-Gault equation for children ≥12 years of age, as follows:

Cockcroft-Gault equation (participants ≥12 years of age):

$$\text{Creatinine clearance (males)} = \frac{(\text{weight in kg}) \times (140 - \text{age})}{(72) \times (\text{creatinine in mg/dL})}$$

Creatinine clearance (females) = 0.85 × the value obtained using the equation above

[b] eGFR ranges taken from published lower-bound standard deviation of age-appropriate means [Brion, L. P., et al 1986] [Schwartz, G. J. 2009] [Sakellaris, G. 2012].

[c] FDA guidance [Food and Drug Administration (CDER) 2014] recommends classifying renal function based on estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2) using the modified Schwartz equation for children <12 years of age, as follows:

$$\text{eGFR} = \frac{K \times (\text{height in cm})}{(\text{creatinine in mg/dL})}$$

K (proportionality constant):

Male child (≥1 year and <12 years): K=0.70

Female child (≥1 year and <12 years): K=0.55

Infant (term <1 year): K=0.45

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic intentional, excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death
b. Is life-threatening
   - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization
   - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. Results in persistent or significant disability/incapacity
   - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
   - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect
   - In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events
   - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
   - Examples of such events include invasive or malignant cancers, 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.

10.3.4 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer.
- Is associated with an overdose.

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:
  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).
  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).
  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the study intervention cause the AE?
- The determination of the likelihood that the study intervention caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form ensures that a medically qualified assessment of causality was performed. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based on the available information.
- **The following components are to be used to assess the relationship between the study intervention and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:
  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention, such as: reliable history, acceptable compliance assessment (infusion

completion verification, pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

- **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?
- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
- **Dechallenge:** Was the study intervention discontinued or dose/exposure/frequency reduced?
  - If yes, did the AE resolve or improve?
  - If yes, this is a positive dechallenge.
  - If no, this is a negative dechallenge.

  (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the study intervention; (3) the study is a single-dose drug study; or (4) study intervention(s) is/are only used 1 time.)
- **Rechallenge:** Was the participant re-exposed to the study intervention in this study?
  - If yes, did the AE recur or worsen?
  - If yes, this is a positive rechallenge.
  - If no, this is a negative rechallenge.

  (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) study intervention(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE STUDY INTERVENTION, OR IF RE-EXPOSURE TO THE STUDY INTERVENTION POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).
  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).

- If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
- Reference Section 8.4.1 for reporting time requirements.

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure email of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile after menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes), and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

10.5.2 Contraceptive Requirements

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to 1 of the following during the protocol-defined time frame in Section 5.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
- Use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.
  - The following are not acceptable methods of contraception:
- Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM).
- Male condom with cap, diaphragm, or sponge with spermicide.

- Male and female condom cannot be used together.
  - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[a,b] • Intrauterine hormone-releasing system (IUS)[b,c] • Nonhormonal intrauterine device (IUD) • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) All sexual partners of the WOCBP must be azoospermic. The participant must provide verbal confirmation of partner azoospermia during Medical History. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.
Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception[b,c] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[b,c] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Acceptable Contraceptive Methods *Failure rate of >1% per year when used consistently and correctly.*
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action - Male or female condom with or without spermicide - Cervical cap, diaphragm, or sponge with spermicide - A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)d
[a] If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive implants are limited to those that inhibit ovulation. [b] Male condoms must be used in addition to female participant's hormonal contraception. [c] IUS is a progestin-releasing IUD. [d] A combination of male condom with either cap, diaphragm, or sponge with spermicide are considered acceptable, but not highly effective, birth control methods.

10.5.3 Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

Not applicable.

10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Disease Definitions and Diagnostic Criteria

10.8.1 HABP/VABP

- Definitions:
  - HABP is an acute infection of the pulmonary parenchyma that is associated with clinical signs and symptoms accompanied by presence of new or progressive infiltrate on chest radiograph occurring in a participant after being hospitalized for more than 48 hours or within 7 days after discharge from hospital. Of note, such participants may or may not require mechanical ventilation (ventilated HABP and nonventilated HABP).
  - VABP is an acute infection of the pulmonary parenchyma that is associated with clinical signs and symptoms accompanied by presence of new or progressive infiltrate on chest radiograph occurring in a participant already receiving mechanical ventilation via an endotracheal tube for a minimum of 48 hours.
- Diagnosis: For a diagnosis of HABP/VABP, participants should have present the following supportive radiographic, clinical, and microbiological findings, with onset of criteria occurring after more than 48 hours of hospitalization or within 7 days after discharge from a hospital (for HABP) or at least 48 hours after mechanical ventilation (for VABP):

  a) Radiographic: Chest radiograph showing the presence of a new or progressive infiltrate(s) characteristic of bacterial pneumonia.

  AND

  b) Clinical: At least 1 of the following clinical findings that support a diagnosis of HABP/VABP:

  - New onset or worsening pulmonary signs and symptoms, such as cough, dyspnea, tachypnea (eg, respiratory rate greater than 25 breaths per minute), expectorated sputum production, or requirement for mechanical ventilation
  - Hypoxemia (eg, a partial pressure of oxygen less than 60 millimeters of mercury while the patient is breathing room air, as determined by arterial blood gas [ABG] or worsening of the ratio of the partial pressure of oxygen to the fraction of inspired oxygen [PaO_2/FiO_2])
  - Need for acute changes in the ventilator support system to enhance oxygenation, as determined by worsening oxygenation (ABG or PaO_2/FiO_2) or needed changes in the amount of positive end-expiratory pressure
  - New onset of suctioned respiratory secretions

  AND

at least 1 of the following clinical findings:

- Fever, defined as body temperature greater than or equal to 38.0°C (100.4°F), or hypothermia, defined as core body temperature less than or equal to 35°C (95.2°F)
- Chills/rigors
- Chest pain
- Total peripheral WBC count greater than or equal to 10,000 cells/mm^3
- Leukopenia with total WBC less than or equal to 4,500 cells/mm^3
- Greater than 15 percent immature neutrophils (bands) noted on peripheral blood smear

AND

c) Microbiological: an appropriate baseline (at or within 48 hours of screening) LRT specimen for Gram stain, culture, and susceptibility testing. See Section 8.2.3.1.1 for additional details.

10.8.2 cIAI

- Definition: Intra-abdominal infection (IAI) is broadly defined as peritoneal inflammation in response to microorganisms, resulting in purulence in the peritoneal cavity. IAI are classified as uncomplicated or complicated based on the extent of infection. cIAI extends beyond the hollow viscus of origin into the peritoneal space and is associated with either abscess formation or peritonitis.
- Diagnosis: For a diagnosis of cIAI, participants must have present the following supportive clinical and microbiological findings. Patients may be enrolled pre-operatively on the basis of compelling preoperative clinical findings as described below OR patients may be enrolled intra- or post-operatively on the basis of operative findings. Surgical intervention includes open laparotomy, laparoscopy, and percutaneous drainage of intra-abdominal abscess.

  Preoperative Enrollment: Patients may be enrolled preoperatively based on the following clinical and microbiological criteria that must be met at screening:

  a) Clinical: at least 1 of the following clinical signs and symptoms of infection:

  - Fever, defined as body temperature greater than or equal to 38.0°C (100.4°F), or hypothermia, defined as core body temperature less than or equal to 35°C (95.2°F)
  - Hypotension

- Abdominal pain, flank pain, or pain caused by cIAI that is referred to another anatomic area such as back or hip
- Tenderness to palpation, rebound tenderness, guarding
- Abdominal mass
- Nausea or vomiting
- Anorexia
- Altered mental status
- WBC count elevated beyond the upper limit of the normal laboratory range or the proportion of band forms of the white blood cell differential count beyond the upper limit of the normal laboratory range

AND

b) Radiographic: Radiographic evidence consistent with intra-abdominal abscess or peritonitis

AND

c) Microbiological: Participants enrolled preoperatively must have an infection-site specimen obtained within 24 hours after the start of IV study intervention. This baseline intra-abdominal specimen is collected from purulent material from an intra-abdominal surgical procedure or percutaneous drainage for culture and susceptibility testing. See Section 8.2.3.1.2 for additional details.

OR

Intra- or Post-operative Enrollment: Patients may be enrolled intra- or post-operatively based on the following visual confirmation (eg, presence of pus within the abdominal cavity) of an intra-abdominal infection and microbiological criteria that must be met at screening:

a) Clinical: at least 1 of the following as evidence of intraperitoneal infection:

- Intra-abdominal abscess, including splenic or liver abscess
- Appendicitis complication by perforation or abscess formation
- Diverticulitis complicated by perforation or abscess formation
- Cholecystitis with evidence of perforation or empyema
- Perforation of the large or small intestine with abscess or fecal contamination

- Gastric or duodenal ulcer perforation
- Peritonitis due to perforated viscus, surgical intervention, or other focus of infection. Spontaneous bacterial peritonitis associated with cirrhosis and chronic ascites are not eligible.

AND

b) Microbiological: Participants enrolled intra- or post-operatively must have had an operative procedure during which an infection-site culture specimen was obtained within 48 hours of screening and prior to the start of IV study intervention. This baseline intra-abdominal specimen is collected from purulent material from an intra-abdominal surgical procedure or percutaneous drainage for culture and susceptibility testing. See Section 8.2.3.1.2 for additional details.

10.8.3 cUTI

- Definition: cUTI is an infection of 1 or more structures in the urinary system in the presence of a functional or anatomical abnormality of the urinary tract or catheterization and includes:
  - Complicated lower UTI (cLUTI): a type of cUTI that does not involve the upper urinary tract
  - Pyelonephritis: a type of cUTI that affects 1 or both kidneys, regardless of underlying abnormalities of the urinary tract

  UTIs are a clinical syndrome characterized by pyuria and a documented microbial pathogen on culture of urine or blood, accompanied by local and systemic signs and symptoms of infection. Establishing a diagnosis of UTI requires both urinalysis results that suggest infection (pyuria and/or bacteriuria) *and* the presence of a uropathogen cultured from a urine specimen obtained by midstream clean catch (MSCC), straight catheter (clean intermittent urethral catheterization), indwelling urethral catheter, or suprapubic aspiration (SPA) [Roberts, K. B. 2011] [Stein, R., et al 2015].

- Diagnosis: For a diagnosis of cUTI (including cLUTI and pyelonephritis), participants must have present the following supportive clinical, anatomical, and microbiological findings:
  a) Clinical:

    - Participants with cUTI (including cLUTI and pyelonephritis) must have at least 2 of the following new or worsening clinical signs and symptoms of cUTI at the Screening Visit:

If <2 years of age:	If 2 to <18 years of age:
- Fever, defined as body temperature greater than or equal to 38.0°C (100.4°F) - Failure to thrive - Recent weight loss - Irritability - Poor feeding - Lack of normal level of activity - Abdominal pain/tenderness on physical examination - Vomiting - Jaundice	- Fever, defined as body temperature greater than or equal to 38.0°C (100.4°F) - Chills or rigors - Dysuria - Urinary urgency - Urinary frequency - New-onset urinary incontinence - Suprapubic pain, flank pain, abdominal pain, or pelvic pain - Suprapubic tenderness or costovertebral angle (CVA) tenderness on physical examination - Nausea or vomiting

IN ADDITION

- Participants with cLUTI must have at least 2 of the above new or worsening clinical signs and symptoms **AND** at least **1** of the following complicating factors:

  - Obstructive uropathy
  - Congenital, functional, or anatomic abnormality of the urogenital tract
  - Temporary indwelling urinary catheter
  - Bladder instrumentation within <24 hours
  - Recurrent UTI (≥2 events within a 12-month period)

AND

Participants with cUTI (including cLUTI and pyelonephritis) must also have pyuria, as determined by MSCC or catheterized (indwelling or straight catheter) urine specimen with ≥10 WBCs per high-power field (hpf) on standard

examination of urine sediment or ≥10 WBCs/mm^3 in unspun urine. The requirement for pyuria may be fulfilled on any urine specimen obtained within 48 hours prior to randomization.

NOTE: If pyuria cannot be determined by urinalysis in a clinically relevant timeframe, a urine dipstick may be used as a rapid diagnostic aid. If urine dipstick is used, a positive test for leukocyte esterase is the preferred indicator for the presence of pyuria.

- If ≥1 year of age: WBC count >10 cells/µL in unspun urine or ≥10 cells/hpf in spun urine; OR
- If <1 year of age: WBC count >5 cells/µL in unspun urine or ≥5 cells/hpf in spun urine

AND

b) Microbiological: Participants with cUTI must have a pretreatment baseline urine culture specimen obtained within 48 hours of screening, prior to the start of IV study intervention, and preferably prior to administration of any potentially therapeutic antibiotics. Specimen is to be obtained by MSCC, indwelling urethral catheter, SPA, or clean intermittent urethral catheterization. Culture results must show ≥10^5 CFU/mL of uropathogen.

NOTE: Participants may be enrolled in this study while urine culture results are still pending. IV study intervention can be started before the investigator knows the results of the baseline urine culture; however, participants who do not have a positive culture result that meets 1 of the above criteria must discontinue study intervention following the negative culture result.

For participants with an indwelling catheter, samples should be collected following the placement of a new catheter. If the placement of a new catheter is contraindicated or is not feasible, specimens should be collected using aseptic techniques with the urine obtained through a properly disinfected collection port. Urine samples obtained from a collection bag are not allowed for the study-qualifying baseline urine culture specimen.

10.9 Appendix 9: Protocol-allowed Comparator Medications by Drug Name

The active comparators listed in the EDC and EDC guidelines for each infection type are as follows (by generic drug name).

10.9.1 HABP/VABP

- Doripenem IV
- Ertapenem IV
- Imipenem IV
- Meropenem IV
- Piperacillin/Tazobactam IV
- Cefepime IV

10.9.2 cIAI

- Doripenem IV
- Ertapenem IV
- Imipenem IV
- Meropenem IV
- Cefotaxime IV
- Ceftazidime IV
- Ceftazidime plus avibactam IV
- Ceftriaxone IV
- Metronidazole IV
- Piperacillin/Tazobactam IV
- Amoxicillin plus clavulanate Oral
- Cefaclor Oral
- Cefprozil Oral
- Cefuroxime Oral
- Cefdinir Oral
- Cefditoren Oral
- Cefixime Oral
- Cefpodoxime Oral
- Ceftibuten Oral

- Ciprofloxacin Oral
- Delafloxacin Oral
- Gemifloxacin Oral
- Levofloxacin Oral
- Moxifloxacin Oral
- Norfloxacin Oral
- Ofloxacin Oral
- Metronidazole Oral

10.9.3 cUTI

- Cefotaxime IV
- Ceftazidime IV
- Ceftazidime plus avibactam IV
- Ceftriaxone IV
- Cefepime IV
- Ciprofloxacin IV
- Meropenem IV
- Amoxicillin plus clavulanate Oral
- Cefadroxil Oral
- Cephalexin Oral
- Cephradine Oral
- Cefaclor Oral
- Cefprozil Oral
- Cefuroxime Oral
- Cefdinir Oral
- Cefditoren Oral
- Cefixime Oral
- Cefpodoxime Oral
- Ceftibuten Oral
- Ciprofloxacin Oral
- Delafloxacin Oral

- Gemifloxacin Oral
- Levofloxacin Oral
- Moxifloxacin Oral
- Norfloxacin Oral
- Ofloxacin Oral
- Nitrofurantoin Oral
- Trimethoprim Oral
- Trimethoprim/Sulfamethoxazole Oral

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
ABG	arterial blood gas
AE	adverse event
ALT	alanine aminotransferase
APaT	All Participants as Treated
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area under the curve
$AUC_{0\text{-}24\ hr}$	area under the plasma concentration-time curve from time zero to 24 hours
BAL	bronchoalveolar lavage
BLI	β-lactamase inhibitor
CAUTI	catheter-associated urinary tract infection
C_{eoi}	concentration at end of infusion
CFU	colony-forming unit
cIAI	complicated intra-abdominal infection
CL	clearance
cLUTI	complicated lower urinary tract infection
C_{max}	maximum concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CR	carbapenem-resistant
CrCl	creatinine clearance
CRF	case report form
CSF	cerebrospinal fluid
CSR	case study report
CT	computed tomography
CTFG	Clinical Trial Facilitation Group
cUTI	complicated urinary tract infection
CVA	costovertebral angle
DILI	drug-induced liver injury
ECI	event of clinical interest
eCRF	electronic case report form
EDC	electronic data collection
eDMC	external Data Monitoring Committee
EEA	European Economic Area
EFU	early follow-up
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EOIV	end of IV therapy
EOT	end of therapy
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDC	fixed-dose combination
$fAUC_{0\text{-}24hr}$/MIC	ratio of the free area under the plasma concentration-time curve to the imipenem/REL minimum inhibitory concentration
GCP	Good Clinical Practice
HABP	hospital-acquired bacterial pneumonia
HIV	human immunodeficiency virus
hpf	high-power field

Abbreviation	Expanded Term
hr	hours
IA(s)	interim analysis(ses)
IAI	intra-abdominal
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICU	intensive care unit
ID	identification
IDSA	Infectious Diseases Society of America
IEC	Independent Ethics Committee
IG	Intervention Group
IMI	imipenem and cilastatin, also referred to as PRIMAXIN® and TIENAM®
IMI/REL	imipenem/cilastatin/relebactam fixed-dose combination, also referred to as MK-7655A
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
KPC	*Klebsiella pneumoniae* carbapenemase
LAM	lactational amenorrhoea method
LFU	late follow-up
LP	lumbar puncture
LRT	lower respiratory tract
M&N	Miettinen and Nurminen
MDR	multi-drug resistance
MIC	minimum inhibitory concentration
MITT	modified intent-to-treat
mMITT	microbiological modified intent-to-treat
mRNA	messenger ribonucleic acid
MRSA	methicillin-resistant *S. aureus*
MSCC	midstream clean catch
O_2	oxygen
OTX	on therapy
PaO_2/FiO_2	ratio of partial pressure of oxygen to the fraction of inspired oxygen
%*f*T>MIC	percentage of time the free imipenem concentration is above the imipenem/REL minimum inhibitory concentration
PI	Package Insert
PICU	pediatric intensive care unit
PIP	Pediatric Investigation Plan
PIP/TAZ	piperacillin/tazobactam
PK	pharmacokinetic(s)
PO	per os (orally)
PTA	Pharmacokinetic-pharmacodynamic target attainment
PTD	patient treatment days
q6h	every 6 hours
q8h	every 8 hours
REL	relebactam, also referred to as MK-7655
SAE	serious adverse event
sSAP	supplemental statistical analysis plan

Abbreviation	Expanded Term
SLAB	supplemental laboratory electronic case report form
SoA	schedule of activities
SOC	System Organ Class
SPA	suprapubic aspiration
SPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reaction
TMP/SMX	trimethoprim-sulfamethoxazole
$t_{1/2}$	Half-life
ULN	upper limit of normal
US	United States
USPI	United States Package Insert
UTI	urinary tract infection
VABP	ventilator-associated bacterial pneumonia
VAP	ventilator-associated pneumonia
VRE	vancomycin-resistant *Enterococcus* spp.
WBC	white blood cell
Vc	volume of distribution for the central compartment
WOCBP	woman/women of childbearing potential

11 REFERENCES

[Addiss, D. G., et al 1990]	Addiss DG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. Am J Epidemiol. 1990 Nov;132(5):910-25.	[04474R]
[Agresti, A. and Coull, B. A. 1998]	Agresti A, Coull BA. Approximate is better than "exact" for interval estimation of binomial proportions. Am Stat 1998;52(2):119-26.	[03NSDW]
[Andersen, S. B., et al 2009]	Andersen SB, Paerregaard A, Larsen K. Changes in the epidemiology of acute appendicitis and appendectomy in Danish children 1996-2004. Eur J Pediatr Surg. 2009 Oct;19(5):286-9.	[0448M2]
[Bachur, R. G. 2001]	Bachur RG, Harper MB. Predictive model for serious bacterial infections among infants younger than 3 months of age. Pediatrics. 2001 Aug;108(2):311-6.	[043WBQ]
[Bader, M. S., et al 2010]	Bader MS, Hawboldt J, Brooks A. Management of complicated urinary tract infections in the era of antimicrobial resistance. Postgrad Med. 2010 Nov;122(6):7-15.	[044QP8]
[Becknell, B., et al 2015]	Becknell B, Schober M, Korbel L, Spencer JD. The diagnosis, evaluation and treatment of acute and recurrent pediatric urinary tract infections. Expert Rev Anti Infect Ther. 2015 Jan;13(1):81-90.	[04L9BT]
[Bedetti, L., et al 2018]	Bedetti L, Marrozzini L, Baraldi A, Spezia E, Iughetti L, Lucaccioni L, et al. Pitfalls in the diagnosis of meningitis in neonates and young infants: the role of lumbar puncture. J Matern Fetal Neonatal Med. In press 2018.	[04ZHDN]

[Bonadio, W. A., et al 1993]	Bonadio WA, Hennes H, Smith D, Ruffing R, Melzer-Lange M, Lye P, et al. Reliability of observation variables in distinguishing infectious outcome of febrile young infants. Pediatr Infect Dis J. 1993 Feb;12(2):111-4.	[043WBW]
[Bradley, J. S. 2002]	Bradley JS. Old and new antibiotics for pediatric pneumonia. Semin Respir Infect. 2002 Mar;17(1):57-64.	[0457Q2]
[Brion, L. P., et al 1986]	Brion LP, Fleischman AR, McCarton C, Schwartz GJ. A simple estimate of glomerular filtration rate in low birth weight infants during the first year of life: noninvasive assessment of body composition and growth. J Pediatr. 1986 Oct;109(4):698-707.	[04JMK0]
[Chastre, J., et al 2003]	Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F, Wermert D, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA. 2003 Nov 19;290(19):2588-98.	[0407FX]
[Chastre, J., et al 2008]	Chastre J, Wunderink R, Prokocimer P, Lee M, Kaniga K, Friedland I. Efficacy and safety of intravenous infusion of doripenem versus imipenem in ventilator-associated pneumonia: a multicenter, randomized study. Crit Care Med 2008;36(4):1089-96.	[03R47S]
[Cheng, C.-Y., et al 2010]	Cheng C-Y, Sheng W-H, Wang J-T, Chen Y-C, Chang S-C. Safety and efficacy of intravenous colistin (colistin methanesulphonate) for severe multidrug-resistant Gram-negative bacterial infections. Int J Antimicrob Agents 2010;35:297-300.	[03RNLP]

[Davis, K. F., et al 2014]	Davis KF, Colebaugh AM, Eithun BL, Klieger SB, Meredith DJ, Plachter N, et al. Reducing catheter-associated urinary tract infections: a quality-improvement initiative. Pediatrics. 2014 Sep;134(3):e857-64.	[04474X]
[DeFrances, C. J., et al 2007]	DeFrances CJ, Cullen KA, Kozak LJ. National hospital discharge survey: 2005 annual summary with detailed diagnosis and procedure data. Vital and Health Statistics 2007;Series 13(165):1-209.	[03QKQH]
[Dellinger, R. P., et al 2013]	Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41(2):580-637.	[03RTJX]
[Dudeck, M. A., et al 2013]	Dudeck MA, Weiner LM, Allen-Bridson K, Malpiedi PJ, Peterson KD, Pollock DA, et al. National Healthcare Safety Network (NHSN) report, data summary for 2012, Device-associated module. Am J Infect Control. 2013 Dec;41(12):1148-66.	[04474Y]
[Elward, A. M., et al 2002]	Elward AM, Warren DK, Fraser VJ. Ventilator-associated pneumonia in pediatric intensive care unit patients: risk factors and outcomes. Pediatrics. 2002 May;109(5):758-64.	[044752]
[European Medicines Agency 2013]	European Medicines Agency. Committee for Human Medicinal Products (CHMP) - Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (EMA/CHMP/351889/2013) [Internet]. London: EMA; 2013. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/11/WC500153953.pdf	[0457YN]

[Falagas, M. E., et al 2005]	Falagas ME, Fragoulis KN, Kasiakou SK, Sermaidis GJ, Michalopoulos A. Nephrotoxicity of intravenous colistin: A prospective evaluation. Int J Antimicrob Ag 2005;26:504-7.	[03RRBK]
[Ferrera, P. C., et al 1997]	Ferrera PC, Bartfield JM, Snyder HS. Neonatal fever: utility of the Rochester criteria in determining low risk for serious bacterial infections. Am J Emerg Med. 1997 May;15(3):299-302.	[043WV0]
[Finnell, S. M., et al 2011]	Finnell SM, Carroll AE, Downs SM; Subcommittee on Urinary Tract Infection. Technical report-Diagnosis and management of an initial UTI in febrile infants and young children. Pediatrics. 2011 Sep;128(3):e749-70.	[043WVF]
[Foglia, E., et al 2007]	Foglia E, Meier MD, Elward A. Ventilator-associated pneumonia in neonatal and pediatric intensive care unit patients. Clin Microbiol Rev. 2007 Jul;20(3):409-25.	[044GPS]
[Food and Drug Administration (CDER) 2014]	Food and Drug Administration (CDER). General clinical pharmacology considerations for pediatric studies for drugs and biological products [Internet]. Silver Spring, MD: U.S. Department of Health and Human Services; 2014. Available from: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425885.pdf.	[04JMPW]
[Food and Drug Administration 2014]	Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry: Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia: developing drugs for treatment [Internet]. Silver Spring, MD: Department of Health and Human Services; 2014 [Updated May 2014]. Available from: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm	[0404ZK]

[Food and Drug Administration 2018]	Food and Drug Administration. Complicated intra-abdominal infections: developing drugs for treatment: guidance for industry. Silver Spring, MD. May 2018.	[04ZPNG]
[Food and Drug Administration 2018]	Food and Drug Administration. Complicated urinary tract infections: developing drugs for treatment: guidance for industry. Silver Spring, MD. June 2018.	[04ZPPS]
[Freire, A. T., et al 2010]	Freire AT, Melnyk V, Kim MJ, Datsenko O, Dzyublik O, Glumcher F, et al. Comparison of tigecycline with imipenem/cilastatin for the treatment of hospital-acquired pneumonia. Diagn Microbiol Infect Dis 2010;68:140-51.	[03RSHR]
[Garnacho-Montero, J., et al 2003]	Garnacho-Montero J, Ortiz-Leyba C, Jimenez-Jimenez FJ, Barrero-Almodovar AE, Garcia-Garmendia JL, Bernabeu-Wittell M, et al. Treatment of multidrug-resistant acinetobacter baumannii ventilator-associated pneumonia (VAP) with intravenous colistin: a comparison with imipenem-susceptible VAP. Clin Infect Dis 2003;36:1111-8.	[03RRBM]
[Gautam, A., et al 2012]	Gautam A, Ganu SS, Tegg OJ, Andresen DN, Wilkins BH, Schell DN. Ventilator-associated pneumonia in a tertiary paediatric intensive care unit: a 1-year prospective observational study. Crit Care Resusc. 2012 Dec;14(4):283-9.	[044NDM]
[Grabe, M., et al 2013]	Grabe M, et al. Guidelines on Urological Infections. Urological Infections - Limited Update March 2013	[04D27M]
[Grohskopf, L. A., et al 2002]	Grohskopf LA, Sinkowitz-Cochran RL, Garrett DO, Sohn AH, Levine GL, Siegel JD, et al. A national point-prevalence survey of pediatric intensive care unit-acquired infections in the United States. J Pediatr. 2002 Apr;140(4):432-8.	[044750]

[Gupta, S., et al 2015]	Gupta S, Boville BM, Blanton R, Lukasiewicz G, Wincek J, Bai C, et al. A multicentered prospective analysis of diagnosis, risk factors, and outcomes associated with pediatric ventilator-associated pneumonia. Pediatr Crit Care Med. 2015 Mar;16(3):e65-73.	[044NDX]
[Hachem, Ray Y., et al 2007]	Hachem RY, Chemaly RF, Ahmar CA, Jiang Y, Boktour MR, Rjaili GA, et al. Colistin Is Effective in Treatment of Infections Caused by Multidrug-Resistant Pseudomonas aeruginosa in Cancer Patients. Antimicrob Agents Chemother 2007;51(6):1905-11.	[03RNLG]
[Hooton, T. M., et al 2010]	Hooton TM, Bradley SF, Cardenas DD, Colgan R, Geerlings SE, Rice JC, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. Clin Infect Dis 2010;50:625-63.	[03RCJ3]
[Hooven, T. A. 2014]	Hooven TA, Polin RA. Healthcare-associated infections in the hospitalized neonate: a review. Early Hum Dev. 2014 Mar;90 Suppl 1:S4-6.	[044NFS]
[Hsu, A. J. 2014]	Hsu AJ, Tamma PD. Treatment of multidrug-resistant Gram-negative infections in children. Clin Infect Dis. 2014 May;58(10):1439-48.	[044M69]
[IB Edition 14 2021]	RECARBRIOTM [US] Investigator's Brochure Edition Number 14, 30-April-2021.	[05PX3X]
[Joshi, M., et al 2006]	Joshi M, Metzler M, McCarthy M, Olvey S, Kassira W, Cooper A. Comparison of piperacillin/tazobactam and imipenem/cilastatin, both in combination with tobramycin, administered every 6 h for treatment of nosocomial pneumonia. Respir Med 2006;100:1554-65.	[03WRG6]

[Kadish, H. A., et al 2000]	Kadish HA, Loveridge B, Tobey J, Bolte RG, Corneli HM. Applying outpatient protocols in febrile infants 1-28 days of age: can the threshold be lowered? Clin Pediatr (Phila). 2000 Feb;39(2):81-8.	[043WHL]
[Kallel, H., et al 2007]	Kallel H, Hergafi L, Bahloul M, Hakin A, Dammak H, Chelly H, et al. Safety and efficacy of colistin compared with imipenem in the treatment of ventilator-associated pneumonia: a matched case-control study. Intensive Care Med 2007;33:1162-7.	[03RNLR]
[Kollef, M. H., et al 2012]	Kollef MH, Chastre J, Clavel M, Restrepo MI, Michiels B, Kaniga K, et al. A randomized trial of 7-day doripenem versus 10-day imipenem-cilastatin for ventilator associated pneumonia. Crit Care 2012;16:1-17.	[03RSHS]
[Markou, Nikolaos, et al 2003]	Markou N, Apostolakos H, Koumoudiou C, Athanasiou M, Koutsoukou A, Alamanos I, et al. Intravenous colistin in the treatment of sepsis from multiresistant Gram-negative bacilli in critically ill patients. Critical care 2003;7(5):R78-R83.	[03RNLK]
[Miettinen, O. and Nurminen, M. 1985]	Miettinen O, Nurminen M. Comparative analysis of two rates. Statistics in Medicine 1985;4:213-26.	[03P76P]
[Niederman, M. S. 2005]	Niederman MS, Craven DE. American Thoracic Society Documents: Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388-416.	[03RTJV]
[Patria, M. F. 2013]	Patria MF, Esposito S. Recurrent lower respiratory tract infections in children: a practical approach to diagnosis. Paediatr Respir Rev. 2013 Mar;14(1):53-60.	[044PDZ]

[Pintado, V., et al 2008]	Pintado V, García San Miguel L, Grill F, Mejía B, Cobo J, Fortún J, et al. Intravenous colistin sulphomethate sodium for therapy of infections due to multidrug-resistant gram-negative bacteria. Journal of Infection 2008;56:185-90.	[03RNLT]
[Pugh, R., et al 2011]	Pugh R, Grant C, Cooke RP, Dempsey G. Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults. Cochrane Database Syst Rev. 2011 Oct 5;(10):CD007577.	[0407FH]
[Reina, R., et al 2005]	Reina R, Estenssoro E, Saenz G, Canales HS, Gonzalvo R, Vidal G, et al. Safety and efficacy of colistin in Acinetobacter and Pseudomonas infections: a prospective cohort study. Intensive Care Med 2005;31:1058-65.	[03RPWC]
[Roberts, K. B. 2011]	Roberts KB. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics. 2011 Sep;128(3):595-610.	[04ZKBF]
[Roeleveld, P. P., et al 2011]	Roeleveld PP, Guijt D, Kuijper EJ, Hazekamp MG, de Wilde RB, de Jonge E. Ventilator-associated pneumonia in children after cardiac surgery in The Netherlands. Intensive Care Med. 2011 Oct;37(10):1656-63.	[044PF7]
[Sakellaris, G. 2012]	Sakellaris G, editior. Essentials in Pediatric Urology. Trivandrum: Research Signpost; c2012. Chapter 2. The development of renal function; p. 9-20.	[04JNTC]
[Schwartz, G. J. 2009]	Schwartz GJ, Work DF. Measurement and estimation of GFR in children and adolescents. Clin J Am Soc Nephrol. 2009 Nov;4(11):1832-43.	[04HDS5]

[Skrupky, L. P., et al 2013]	Skrupky LP, Tellor BR, Mazuski JE. Current strategies for the treatment of complicated intraabdominal infections. Expert Opin Pharmacother. 2013 Oct;14(14):1933-47.	[04439N]
[Solomkin, J. S., et al 2010]	Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJC, Baron EJ, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the surgical infection society and the infectious diseases society of America. Clin Infect Dis 2010;50:133-64.	[03RBW3]
[Stein, R., et al 2015]	Stein R, Dogan HS, Hoebeke P, Kocvara R, Nijman RJ, Radmayr C, et al. Urinary tract infections in children: EAU/ESPU guidelines. Eur Urol. 2015 Mar;67(3):546-58.	[04L9CG]
[Stein, R., et al 2015]	Stein R, Dogan HS, Hoebeke P, Kocvara R, Nijman RJM, Radmayr C, et al. Urinary tract infections in children: EAU/ESPU guidelines. Eur Urol. 2015;67:546-58.	[04ZKBG]
[Summary of Product Characteristics 2011]	Summary of Product Characteristics (SmPC), Labelling and Package Leaflet: Tienam 500 mg/500 mg powder for solution for infusion: Jun 2011.	[04Z47G]
[Torres, A., et al 2000]	Torres A, Bauer TT, León-Gil C, Castillo F, Alvarez-Lerma F, Martínez-Pellús A, et al. Treatment of severe nosocomial pneumonia: a prospective randomised comparison of intravenous ciprofloxacin with imipenem/cilastatin. Thorax 2000;55(12):1033-9.	[03R482]

[U.S. Food and Drug Administration 2018]	U.S. Food and Drug Administration. Safety alerts for human medical products [Internet]. Silver Spring (MD): U.S. Department of Health and Human Services. Fluoroquinolone antibiotics: FDA requires labeling changes due to low blood sugar levels and mental health side effects; 2018 Jul 10 [cited 2018 Aug 13]; [about 3 screens]. Available from: https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm612979.htm.	[050080]
[U.S. Prescribing Information 2017]	U.S. Prescribing Information: PRIMAXIN (imipenem and cilastatin) for Injection, for intraveous use: 2017.	[04YYBX]
[West, M., et al 2003]	West M, Boulanger BR, Fogarty C, Tennenberg A, Wiesinger B, Oross M, et al. Levofloxacin compared with imipenem/cilastatin followed by ciprofloxacin in adult patients with nosocomial pneumonia: a multicenter, prospective, randomized, open-label study. Clin Ther 2003;25(2):485-506.	[03R484]
[Zorc, J. J., et al 2005]	Zorc JJ, Kiddoo DA, Shaw KN. Diagnosis and management of pediatric urinary tract infections. Clin Microbiol Rev. 2005 Apr;18(2):417-22.	[044G96]