

<b>Official Protocol Title:</b>	A Phase 1b, Open-label, Single-dose Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of MK-7655A in Pediatric Subjects From Birth to Less Than 18 Years of Age With Confirmed or Suspected Gram-negative Infections
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**TITLE:**

A Phase 1b, Open-label, Single-dose Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of MK-7655A in Pediatric Subjects From Birth to Less Than 18 Years of Age With Confirmed or Suspected Gram-negative Infections

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**DOCUMENT HISTORY**

<b>Document</b>	<b>Date of Issue</b>	<b>Overall Rationale</b>
MK-7655A-020-00	15-NOV-2016	Original Protocol
MK-7655A-020-01	11-JAN-2019	Amendment 1 (Global) Primary reasons for the amendment: <ul style="list-style-type: none"><li>• Allow enrollment of subjects who may have neonatal hyperbilirubinemia within 24 hours of birth that is part of a normal physiologic process.</li><li>• Remove weight-based exclusion criterion for Cohorts 4 and 5.</li></ul>
MK-7655A-020-02	22-AUG-2019	Amendment 2 (Global) Primary reason for the amendment: <ul style="list-style-type: none"><li>• Allow enrollment into Cohort 5 of subjects who are at least 37 weeks postmenstrual age at the time of screening, regardless of their actual gestational age at birth.</li></ul>

**SUMMARY OF CHANGES**

**PRIMARY REASON(S) FOR THIS AMENDMENT:**

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.1.2	Subject Inclusion Criteria	Inclusion Criterion #4: Revised to allow enrollment into Cohort 5 of subjects who are at least 37 weeks postmenstrual age at the time of screening.	Eligible subjects will not be excluded from Cohort 5 based on gestational age at birth, as long as their postmenstrual age at the time of screening is at least 37 weeks.

**ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:**

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
2.1 2.2 4.2.2.1 5.2.1.1 5.2.1.2.1 5.2.2 8.7	Trial Design Trial Diagram Starting Dose for This Trial Dose Selection (Preparation) Dose Modifications and Decisions After Interim Reviews Timing of Dose Administration Interim Reviews for Potential Dose Adjustment	Updated text to reflect a) completion of Cohort 4 interim review and resulting dose modifications, as previously communicated via Protocol Clarification Letter, and b) completion of enrollment into Cohort 4.	Revised to incorporate summary of dose modifications implemented after the interim review after 50% enrollment in Cohort 4.

## 1.0 TRIAL SUMMARY

Abbreviated Title	A Single-dose Pharmacokinetics Study of MK-7655A in Pediatric Subjects
Sponsor Product Identifiers	MK-7655A (imipenem/cilastatin/relebactam [IMI/REL]) Generic Name: N/A
Trial Phase	Phase 1b
Clinical Indication	Treatment of bacterial infections in pediatric populations
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	MK-7655A (IMI/REL)
Number of trial subjects	Approximately 44 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 3 years from the time the first subject signs the informed consent/assent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial for up to 18 days from the time the subject's parent or legally acceptable representative signs the informed consent/assent form through the final contact. After a screening phase of up to 2 days, each subject will receive 1 dose of IMI/REL. After the single dose, each subject will be followed for 14 (+2) days for adverse events.

A list of abbreviations used in this document can be found in Section 12.4 – List of Abbreviations.

## 2.0 TRIAL DESIGN

### 2.1 Trial Design

This is an open-label, noncomparative study of a single intravenous (IV) dose of MK-7655A (a fixed-dose combination of imipenem/cilastatin/relebactam, hereafter referred to as IMI/REL) in male and female pediatric subjects from birth to less than 18 years of age receiving standard-of-care antibacterial therapy for treatment of a confirmed or suspected Gram-negative bacterial infection.

A minimum of 44 subjects will be enrolled, each into 1 of the following 5 pediatric age cohorts:

- Cohort 1: Adolescents (age 12 to <18 years); at least 6 subjects
- Cohort 2: Older children (6 to <12 years); at least 6 subjects
- Cohort 3: Younger children (2 to <6 years); at least 6 subjects
- Cohort 4: Infants and toddlers (3 months to <2 years); at least 8 subjects, at least 4 of whom are <1 year of age

- Cohort 5: Neonates and young infants (birth to <3 months); at least 18 subjects, who will be further divided into the following age subcohorts:
  - 4 weeks to <3 months of age; at least 6 subjects
  - 1 to <4 weeks of age; at least 6 subjects
  - <1 week of age; at least 6 subjects

All subjects will receive a single dose of IMI/REL administered via IV infusion at the doses specified in [Table 2](#) of Section 5.2 – Trial Treatments. The initial dose for Cohorts 1, 2, and 3 was IMI/REL 15/7.5 mg/kg, and single IV doses for all cohorts did not exceed the adult maximum dose of 500 mg IMI and 250 mg REL. The study design is depicted as a trial diagram in Section 2.2 – Trial Diagram.

For Cohorts 1, 2, and 3, enrollment was initiated in parallel, and an interim review was conducted in each age cohort after the first 3 (50%) subjects were enrolled, at which point, enrollment in that cohort was paused.

Enrollment in each cohort would continue past the third subject without dose modification until all 6 subjects were enrolled in Cohorts 1, 2, and 3 if the following occurred:

1. The interim review demonstrated that the selected initial dose was suitable based on pharmacokinetic (PK) target attainment that was similar to that in adults for a given age cohort (details in Section 5.2.1.2 – Dose Modification), and
2. The dose demonstrated an acceptable safety profile in the exposed cohort, as described in Section 5.2.1.2 – Dose Modification.

Alternatively, enrollment in each cohort would continue with a dose modification based on Section 5.2.1.2 if the following occurred:

1. The interim review revealed a suboptimal (ie, too high or too low) initial dose based on inadequate (ie, too high or too low) PK target attainment relative to adults for a given age cohort (details in Section 5.2.1.2 – Dose Modification), or
2. The safety profile was not acceptable.

Dose modifications following the interim reviews in Cohorts 1 through 3 are described in Section 5.2.1.2.1.

When enrollment of all 6 subjects each in Cohorts 1, 2, and 3 was completed, a second interim review was performed in which aggregated data from Cohorts 1, 2, and 3 was used to (1) develop and refine a pediatric population PK model and conduct simulations to evaluate PK target attainment, and (2) assess whether the safety profile was acceptable for each age cohort. The findings from the second interim review were used to inform the proposed initial doses for Cohorts 4 and 5, which is 10/5 mg/kg IMI/REL. Subject enrollment of Cohorts 4 and 5 was initiated in parallel.

For Cohorts 4 and 5, an interim review will be conducted in each age cohort after the first 4 (50%) subjects are enrolled in Cohort 4 and the first 9 (50%) subjects are enrolled in Cohort 5 (regardless of subcohort), at which point, enrollment in that cohort will pause.

Enrollment will continue past the fourth subject in Cohort 4 and the ninth subject in Cohort 5 without dose modification if the following occurs:

1. The interim review demonstrates that the selected initial dose is suitable based on PK target attainment that is similar to that in adults for a given age cohort (details in Section 5.2.1.2 – Dose Modification), and
2. The dose demonstrates an acceptable safety profile in the exposed cohort, as described in Section 5.2.1.2 – Dose Modification.

Alternatively, enrollment in each cohort will continue with a dose modification based on Section 5.2.1.2 – Dose Modification if the following occurs:

1. The interim review reveals a suboptimal (too high or too low) initial dose based on inadequate (too high or too low) PK target attainment relative to adults for a given age cohort (details in Section 5.2.1.2 – Dose Modification), or
2. The safety profile is not acceptable.

When enrollment into Cohorts 4 and 5 has been completed, a final analysis of PK and safety data will be performed with aggregated data from Cohorts 1 through 5 to refine the optimal dosing for pediatric subjects based on PK target attainment and an acceptable safety profile.

At the time of this protocol amendment (-02), enrollment into Cohort 4 has been completed. Dose modifications following the interim review (ie, after achieving 50% enrollment) in Cohort 4 are described in Section 5.2.1.2.1.

Any dose modifications for Cohort 5 will be selected and communicated as described in Section 5.2.1.2 – Dose Modification and will not exceed the single IV dosage of IMI/REL 500/250 mg.

For each subject, PK parameters will be assessed for up to 6 hours and safety parameters will be assessed for up to 24 hours following the single IV dose of IMI/REL. Subjects will have a safety follow-up visit or telephone contact 14 (+2) days after the infusion.

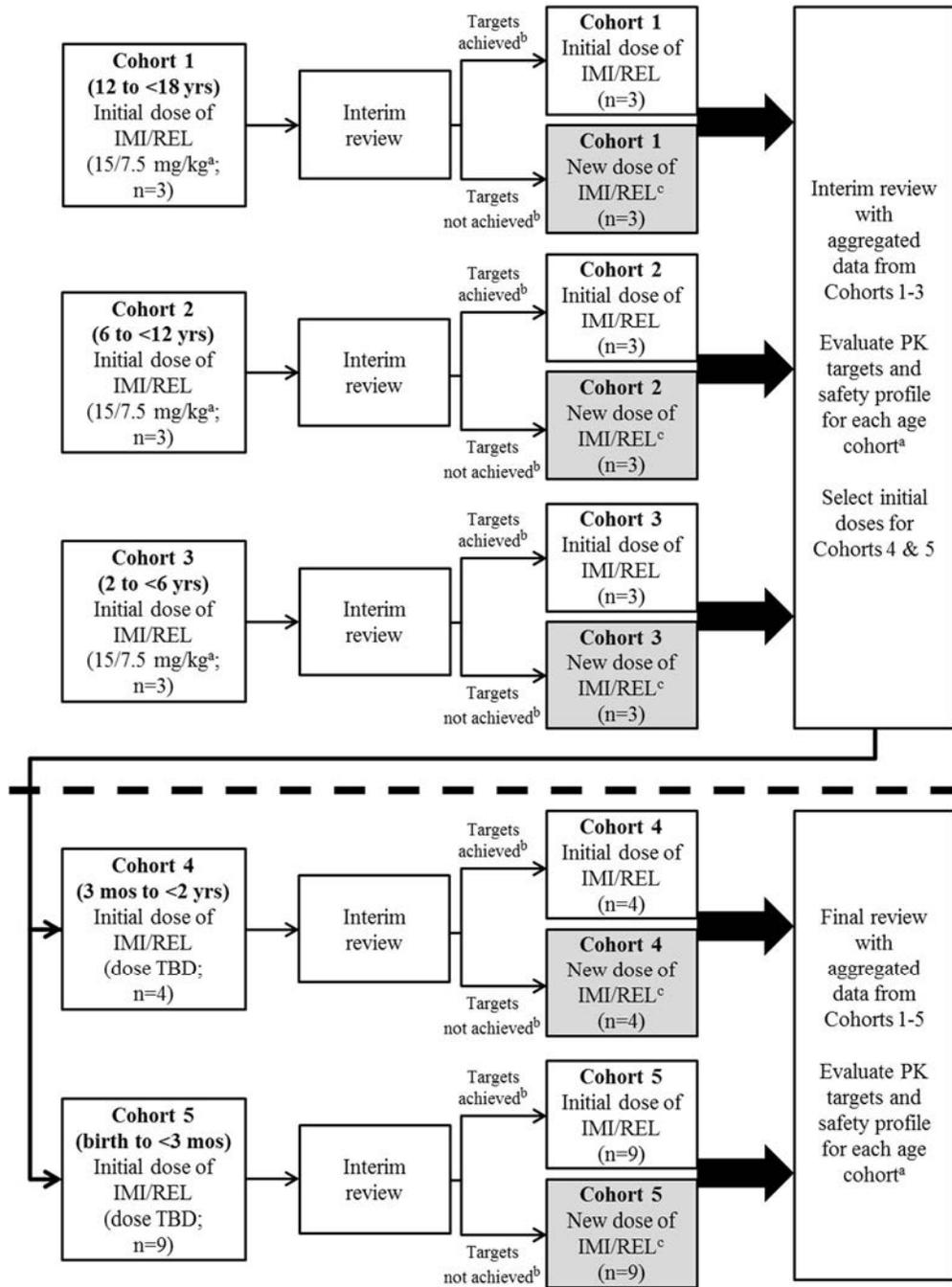
Each subject will participate in the trial for up to 18 days from the time the subject's parent or legally acceptable representative (LAR) signs the informed consent form through the final contact. This includes a screening phase of up to 2 days before receiving a single dose of IMI/REL, and then a follow-up period of 14 (+2) days.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

## **2.2 Trial Diagram**

The trial design is depicted in [Figure 1](#).

Figure 1 Schematic of Study Design for Study MK-7655A-020



Abbreviations: IMI/REL: imipenem/cilastatin/relebactam; mos: months; PK: pharmacokinetic; TBD: to be determined; yrs: years

- Will not exceed a single IV dose of IMI/REL 500/250 mg.
- The criteria for PK and safety target achievement are described in Section 5.2.1.2 – Dose Modification.
- New doses of IMI/REL will be selected and communicated as described in Section 5.2.1.2 – Dose Modification and will not exceed the single IV dosage of IMI/REL 500/250 mg. Dose modifications and decisions following the interim reviews in Cohorts 1 through 4 are described in Section 5.2.1.2.1.

### 3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

#### 3.1 Primary Objective(s) & Hypothesis(es)

**Objective:** To obtain plasma PK data and characterize the PK profile of imipenem, cilastatin, and relebactam (REL) following administration of a single IV dose of IMI/REL in pediatric subjects from birth to less than 18 years of age receiving standard-of-care antibacterial therapy for a confirmed or suspected Gram-negative bacterial infection.

**Hypothesis:** No formal hypothesis testing will be performed for this objective.

#### 3.2 Secondary Objective(s) & Hypothesis(es)

**Objective:** To evaluate the safety and tolerability profile of a single IV dose of IMI/REL in pediatric subjects from birth to less than 18 years of age receiving standard-of-care antibacterial therapy for a confirmed or suspected Gram-negative bacterial infection.

### 4.0 BACKGROUND & RATIONALE

#### 4.1 Background

Refer to the Investigator's Brochure (IB) for detailed background information on MK-7655A.

##### 4.1.1 Pharmaceutical and Therapeutic Background

MK-7655 (relebactam, referred to as REL) is a parenteral (IV), small-molecule  $\beta$ -lactamase inhibitor (BLI), which is being developed as a fixed-dose combination in a single vial with imipenem/cilastatin (referred to as IMI) for the treatment of infections caused by Gram-negative bacteria. Throughout this document, the fixed-dose combination of imipenem/cilastatin/relebactam (MK-7655A) is referred to as IMI/REL.

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

Relebactam represents a new generation of BLIs to combat evolving clinical resistance and to maintain the usefulness of the  $\beta$ -lactam class of antibiotics. Relebactam is an inhibitor of Ambler class A and class C BLIs. This BLI has sub-micromolar potency for AmpC, a class C  $\beta$ -lactamase responsible for resistance in a majority of imipenem-resistant *Pseudomonas aeruginosa*. In addition, REL is active against the class A KPC  $\beta$ -lactamase present in some Enterobacteriaceae, including *Klebsiella* strains, as well as against many other class A and C  $\beta$ -lactamases. Relebactam has no activity against the class B metallo- $\beta$ -lactamases (including

NDM-1, IMP, or VIM-containing strains) or class D  $\beta$ -lactamases (including OXA-producing strains).

#### **4.1.2 Preclinical and Clinical Trials**

##### **4.1.2.1 Preclinical Trials**

Preclinical data, including in vitro microbiological studies with imipenem-resistant clinical isolates of *P. aeruginosa* and KPC-producing organisms, as well as in vivo infection models with imipenem-resistant *P. aeruginosa* and *K. pneumoniae*, suggest that REL, in combination with IMI, has the potential to fulfill a significant and growing medical need by providing a next-generation BLI to combat severe Gram-negative bacterial infections. Preclinical toxicity studies in rats and monkeys have demonstrated that REL is generally well tolerated. There was no evidence of adverse effects of REL as a single agent on cardiovascular, central nervous system, and respiratory function in well-characterized preclinical safety pharmacology models. In monkeys, reversible renal tubular degeneration was seen in monkeys at 7-fold the therapeutic exposure at 250 mg every 6 hours; however, no evidence of renal tubular epithelial degeneration or any other form of renal injury was detected up to 3X the clinical exposure after 3 months of repeated dosing. Combination studies conducted in monkeys demonstrate that dosing with REL and IMI at 1X the projected therapeutic exposure was well tolerated, and antemortem and postmortem findings were similar to monkeys treated with IMI alone, demonstrating that toxicity is not exacerbated by the combination. In addition, no evidence of renal toxicity has been observed in clinical studies.

##### **4.1.2.1.1 Preclinical Juvenile Toxicity Studies**

Results from preclinical juvenile toxicity studies in rats have demonstrated that the no-observed-effect level for REL in juvenile rats was  $\geq 450$  mg/kg/day. Relebactam was administered to rats subcutaneously (postnatal day 14 to 34) or intravenously (postnatal day 35 to 56/57) once daily at doses of 0, 65, 200, or 450 mg/kg/day from postnatal week 3 through postnatal week 9. There were no REL-related findings up to the maximum feasible dose of 450 mg/kg/day. Histomorphologic findings related to repeated IV administration were present at comparable incidences between control and REL-treated animals.

##### **4.1.2.2 Phase 1 Clinical Trials**

To date, REL has been evaluated in approximately 232 individuals who have received at least 1 dose of REL across 7 completed Phase 1 studies (PN001, PN002, PN005, PN007, PN009, PN012, and PN019). Healthy young and elderly adults of both sexes and adults of varying degrees of renal insufficiency have been studied, including patients with end-stage renal disease on hemodialysis.

Unblinded safety data from the Phase 1 studies have demonstrated that single and multiple IV doses of REL have been generally safe and well tolerated throughout the dose ranges tested and across the various subject populations. In PN009 (a standard thorough QTc study evaluating the effect of REL on the QTc interval), a suprathreshold dose of REL did not prolong the QTc interval to a clinically meaningful extent and no risk of cardiac repolarization prolongation was identified.

In PN001, cases of mild elevations in hepatic transaminases above the upper limit of normal range (ULN) were observed in the multiple-dose treatment arms in which REL was coadministered with IMI. Elevations were also seen at similar frequencies in subjects receiving IMI alone. None of the liver transaminase elevations in these subjects were associated with clinical manifestations. The elevations were not dose-related and were reversible after discontinuation of dosing. Generally mild elevations in hepatic transaminases were also observed in Japanese subjects receiving multiple doses of REL in PN012. Similar to observations in PN001, the increases in alanine aminotransferase (ALT)/aspartate aminotransferase (AST) resolved after completion of dosing. Elevations have not been observed in subjects administered single or multiple doses in PN002, PN005, PN007, or single doses in PN009.

Pharmacokinetic data from Phase 1 studies demonstrate the following:

- REL exposures increase proportionally with dose; doses at 125 mg and above adequately achieved and exceeded the identified REL PK target of area under the concentration time curve ( $AUC_{0-\infty}$ )  $\geq 37.5$   $\mu\text{M}\cdot\text{hr}$ .
- For all age and gender comparisons, the 90% confidence intervals for the geometric mean ratios of  $AUC_{0-\infty}$  for REL, imipenem, and cilastatin fell completely within the (0.50 to 2.00) target interval. Therefore, no dose adjustments are recommended based on age or gender.
- PK profiles of REL, imipenem, and cilastatin in healthy Japanese subjects were similar to historical data obtained from non-Japanese subjects.
- PK data from a study of renal-impaired subjects (PN005) were consistent with expectations given that REL, imipenem, and cilastatin are cleared almost entirely renally in healthy subjects. Plasma clearance, terminal half-life ( $t_{1/2}$ ), and  $AUC_{0-\infty}$  were significantly and similarly altered for each of these 3 analytes when comparing subjects with renal impairment to their healthy matched control subjects.
- REL and imipenem penetrate to a similar extent into the extracellular (epithelial lining fluid) of the lung.
- Supratherapeutic levels of REL had no impact on population-specific QTc.
- REL has low potential for any clinically meaningful drug-drug interactions.

#### **4.1.2.3 Phase 2 Clinical Trials**

To date, coadministration of IMI and REL has been evaluated in 2 Phase 2 randomized, double-blind, multicenter, comparative studies evaluating the safety, tolerability, and efficacy of IMI + REL versus IMI alone in adults with complicated intra-abdominal infection (cIAI) (PN004; 351 subjects total) and in adults with complicated urinary tract infection (cUTI) including pyelonephritis (PN003; 302 subjects total). In each study, subjects were randomized in a 1:1:1 ratio to 1 of 3 treatment groups: (1) IMI + REL (250 mg), (2) IMI + REL (125 mg), or (3) IMI + placebo (to REL).

The primary efficacy analysis for each study indicates that treatment with either 250 mg or 125 mg of IMI + REL is at least as effective as IMI alone as measured by the proportion of

subjects with favorable clinical (PN004) or microbiological (PN003) response at discontinuation of IV study therapy. Specifically, in PN004, the proportion of subjects in the primary analysis population with a favorable clinical response was 96.3% (78/81) in subjects who received IMI + REL (250 mg), 98.8% (85/86) in subjects who received IMI + REL (125 mg), and 95.2% (79/83) in subjects who received IMI + placebo. In PN003, the proportion of subjects in the primary analysis population with a favorable microbiological response was 95.5% (64/67) in subjects who received IMI + REL (250 mg), 98.6% (70/71) in subjects who received IMI + REL (125 mg), and 98.7% (74/75) in subjects who received IMI + placebo.

The incidence rate of adverse experiences observed in subjects in studies PN004 and PN003 who received either dose of IMI + REL (either the 125 mg or the 250 mg dose of REL) was generally comparable to that observed in subjects who received IMI + placebo. No evidence of significant renal toxicity or hepatotoxicity was observed. Given the mild elevations in hepatic transaminases observed in PN001 (Section 4.1.2.2), close monitoring for transaminase elevations was included in PN004 and PN003. As part of this monitoring, the following 2 prespecified events of clinical interest (ECIs) triggered staged evaluation and monitoring of subjects with these elevations: (1) confirmed AST or ALT  $\geq 5 \times$  ULN, and (2) ALT or AST  $\geq 3 \times$  ULN and total bilirubin  $\geq 2 \times$  ULN and, at the same time, alkaline phosphatase  $< 2 \times$  ULN. These ECIs were experienced by a small number of subjects in each study (no more than 2 subjects in a given treatment group per study), and in both studies, there were no statistically significant differences in the percentage of subjects meeting the definition of either ECI between either of the 2 IMI + REL groups versus the IMI + placebo group.

#### **4.1.2.4 Phase 3 Clinical Trials**

One completed pivotal Phase 3 study (PN013) evaluated the safety and efficacy of the fixed-dose combination IMI/REL versus comparator (colistin [in the form of colistimethate sodium, CMS] + IMI) in 50 subjects with hospital-acquired or ventilator-associated bacterial pneumonia (HABP/VABP), cIAI, or cUTI caused by imipenem-nonsusceptible Gram-negative bacterial infections.

In PN013, IMI/REL was at least as efficacious as CMS + IMI, as supported by the results of the primary and secondary efficacy endpoints as follows:

- The primary efficacy endpoint of favorable overall response was achieved by a comparable percentage of subjects who received IMI/REL and CMS + IMI.
- Favorable clinical response was achieved by a higher percentage of subjects who received IMI/REL than subjects who received CMS + IMI at all time points assessed.
- All-cause mortality was experienced by a lower percentage of subjects who received IMI/REL than subjects who received CMS + IMI.

In addition, results from PN013 demonstrated that treatment with IMI/REL was well tolerated in critically ill subjects and had a more favorable safety profile than treatment with CMS + IMI. In addition, treatment with IMI/REL exhibited a more favorable renal safety profile than treatment with CMS + IMI, as demonstrated by a lower incidence of

treatment-emergent nephrotoxicity (a reported side effect of colistin) in subjects who received IMI/REL.

### **4.1.3 Ongoing Clinical Trials**

The following studies in adults are currently ongoing:

- Two Phase 3 studies to evaluate the safety and efficacy of IMI/REL compared with that of piperacillin/tazobactam in adult subjects with HABP/VABP (Protocol 014 [PN014], which was initiated in early 2016 [first subject enrolled 28-JAN-2016], and Protocol 016 [PN016], which was initiated in 2018 [first subject enrolled 18-SEP-2018]. PN016 is being conducted to support IMI/REL registration in China).
- A Phase 3 study to evaluate the safety and efficacy of IMI/REL in Japanese adult subjects with cIAI or cUTI (Protocol 017 [PN017], which was initiated in late 2017 [first subject enrolled 04-OCT-2017]). As of January 2019, enrollment was complete, but the final Clinical Study Report was not available.

### **4.1.4 Imipenem/Cilastatin Clinical Experience in Pediatric Populations**

There has been considerable experience with the use of IMI in both adults and pediatric patients since its initial approval over 30 years ago. Imipenem/cilastatin is currently registered and approved in 106 countries. As of 27-JUN-2018, an estimated 35,853,953 patients have been treated with IMI. To date, approximately 2,332 patients (including 223 pediatric subjects) have been exposed to IMI alone or as part of an active comparator regimen in clinical trials conducted by the Sponsor. The 2 pediatric clinical trials conducted by the Sponsor were open-label studies to evaluate the efficacy, safety, tolerability, and PK of IMI in hospitalized pediatric subjects with serious bacterial infections, including intra-abdominal, urinary tract, and respiratory tract infections. Imipenem/cilastatin was efficacious and generally well tolerated in both studies.

## **4.2 Rationale**

### **4.2.1 Rationale for the Trial and Selected Subject Population**

This is the first study in support of the pediatric development of IMI/REL for the treatment of bacterial infections caused by Gram-negative bacteria, including HABP, VABP, cUTI, and cIAI. Overall, the pathogenesis, microbiology, and treatment of these diseases are similar in pediatric patients and in adults.

Increasingly, multidrug resistant (MDR) Gram-negative bacteria, especially extended spectrum  $\beta$ -lactamase-producing organisms and carbapenem-resistant organisms, are becoming a worldwide problem in both adult as well as pediatric patients. Multidrug resistance severely limits the utility of currently available antibacterials. Although new and effective antibacterials have been introduced to combat MDR Gram-positive organisms, clinicians have been forced to utilize older drugs with known limitations in the treatment of resistant Gram-negative pathogens, most notably those with carbapenem resistance. Due to the absence of effective and tolerable antibacterials, infections caused by carbapenem-resistant Gram-negative organisms have a high mortality rate. Even with

treatment using last-resort therapies such as colistin, mortality rates in critically ill patients with MDR pathogens, including carbapenem-resistant pathogens, range from 16% up to as high as 60% [1, 2, 3, 4, 5].

As with adults, infections caused by extended spectrum  $\beta$ -lactamase-producing organisms in pediatric patients are associated with longer hospital stays, frequent complications, and increased mortality, at higher than adult rates in certain regions [6, 7, 8]. Pediatric patients are particularly vulnerable to MDR Gram-negative pathogens due to lack of broad-spectrum antibiotics approved for use in pediatric patients. For treatment of carbapenem-resistant Enterobacteriaceae infections in pediatric patients, there are few treatment alternatives, such as aminoglycoside monotherapy, fluoroquinolones, trimethoprim-sulfamethoxazole, fosfomycin, and nitrofurantoin (mostly for treatment of uncomplicated urinary tract infection). Many of these antibiotics 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 owing to osteoarticular side-effects observed in animal models [9].

As treatment options are limited for MDR infections, and given that there are fewer antibiotics approved for use in pediatric patients as well as the dearth of clinical trials conducted in pediatric patients, the problem is even more critically important to address [9]. Carbapenems are the mainstay of treatment of MDR Gram-negative infections; therefore, the emergence of carbapenem-resistant organisms in recent years is particularly worrisome [10]. The addition of REL to IMI to restore IMI susceptibility for pathogens that produce class A and C  $\beta$ -lactamases therefore addresses an area of growing unmet medical need. Furthermore, IMI/REL is unique among  $\beta$ -lactam/BLI combinations in development due to the long history of pediatric safety and efficacy (Section 4.1.4 – Imipenem/Cilastatin Clinical Experience in Pediatric Populations) and the broad spectrum of activity of the  $\beta$ -lactam compound.

The current United States (US) Food and Drug Administration guidance document for pediatric PK studies focuses on appropriate dosing in the pediatric population based on PK data [11]. The PK of a drug in the pediatric population usually cannot be precisely predicted from PK or clinical studies of adult subjects; rather, specific PK studies in pediatric subjects are needed to determine appropriate pediatric dosing. Thus, the current study will be conducted to investigate the PK and safety of a single IV dose of IMI/REL in pediatric subjects from birth to <18 years of age receiving standard-of-care antibacterials for treatment of confirmed or suspected Gram-negative bacterial infection. The current study will be conducted using 5 age cohorts, with the predominance of subjects in the youngest age cohort, in accordance with guidance from the Food and Drug Administration and the European Medicines Agency (EMA). The information from this study will be used to determine appropriate dosing regimens for a subsequent efficacy study of IMI/REL in a pediatric population.

## **4.2.2 Rationale for Dose Selection/Regimen/Modification**

### **4.2.2.1 Starting Dose for This Trial**

The initial dose of IMI for pediatric subjects in Cohorts 1 through 3 in this study was 15 mg/kg, as designated in the current IMI label (PRIMAXIN® and TIENAM®). The dosing ratio of 2:1 for IMI:REL that is used in adult Phase 2 and 3 trials is used in the current trial. Thus, the initial dose of REL for pediatric subjects in Cohorts 1 through 3 was 7.5 mg/kg. The initial doses were modified (maintaining the 2:1 IMI:REL dosing ratio) based on interim reviews in each age cohort, per the criteria described in Section 5.2.1.2 – Dose Modification. The dose modifications for Cohorts 1 through 3 are described in Section 5.2.1.2.1.

The initial dose of IMI/REL for pediatric subjects in Cohorts 4 and 5 was selected based on updated PK modeling and simulation analyses, after incorporating observed PK data from Cohorts 1 through 3 during the second interim review (Section 5.2.1.2.1). For Cohort 4, the initial dose of 10/5 mg/kg was modified based on the interim review as described in Section 5.2.1.2.1. For Cohort 5, the initial dose of 10/5 mg/kg may later be modified (maintaining the 2:1 IMI:REL dosing ratio) based on subsequent interim reviews in that age cohort.

### **4.2.2.2 Maximum Dose/Exposure for This Trial**

As described in Section 5.2.1.2 – Dose Modification, the doses for each age cohort in this study may be modified based on results of observed PK data from interim reviews. The final pediatric doses will not exceed the dosage currently under study for adult subjects in 2 separate Phase 3 trials (ie, maximum single IV dose of IMI/REL 500/250 mg).

### **4.2.2.3 Rationale for Dose Interval and Trial Design**

A single IV dose of IMI/REL will be administered to each subject in this study. A single-dose rather than a multiple-dose study design was selected from the observed PK properties of IMI/REL in adults. 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 subjects.

## **4.2.3 Rationale for Endpoints**

### **4.2.3.1 Pharmacokinetic/Pharmacodynamic Endpoints**

Based on established literature in the field and data from the adult development program, efficacy of IMI/REL is driven by the time spent above the minimum inhibitory concentration (TMIC) within the dosing interval for imipenem and by drug exposure (as measured by AUC) 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 trial are the same as those for adults. For REL, exposure is the metric of interest, with a target of  $AUC_{0-\infty} \geq 37.5 \mu\text{M}\cdot\text{hr}$  (and  $\leq 200 \mu\text{M}\cdot\text{hr}$ ) after single-dose IV administration of IMI/REL. For imipenem, the target is for subjects to have TMIC of  $\geq 30\%$  for relevant minimum inhibitory concentrations of interest (and  $AUC_{0-\infty} \leq 250 \mu\text{M}\cdot\text{hr}$ ). Doses

of IMI/REL associated with this exposure and TMIC have been established as being safe and efficacious in adults.

Plasma concentrations of REL, imipenem, and cilastatin will be determined. The REL and imipenem data will be used to develop a pediatric population PK model, using the adult model as a starting point; the model will then be used in simulations to determine suitable dosing regimens for subsequent and separate pediatric clinical efficacy trials. The PK properties of cilastatin based on data from this trial will also be described.

#### Rationale for PK Sampling Scheme

Pharmacokinetic sampling will be conducted in each age cohort, taking into consideration the likely minimum body weight of each age cohort and recommended limits on pediatric blood sampling.

Four PK samples per subject will be collected in each of the age cohorts as follows:

1. First PK sample: predose sample taken within 30 minutes before the start of study drug infusion.
2. Second PK sample: collected within 10 minutes after the end of study drug infusion.
3. Third PK sample:
  - Cohorts 1 through 4: obtained 1.5 to 2.5 hours after the start of study drug infusion.
  - Cohort 5: obtained 2 to 5 hours after the start of study drug infusion.
4. Fourth PK sample:
  - Cohorts 1 through 4: obtained 4.5 to 6 hours after the start of study drug infusion.
  - Cohort 5: obtained 6 to 12 hours after the start of study drug infusion.

All PK samples must be drawn within the specified time windows, and the actual sampling times must be documented. The first PK sample establishes a baseline and will allow for evaluation of bioanalytical interference (ie, to ensure there is no analyte of interest detected before dosing). The second PK sample will be used to determine the maximum observed plasma concentration ( $C_{max}$ ). The third and fourth PK samples will provide data during the elimination phase of the study drug and thus, will allow characterization of the selected PK parameters,  $AUC_{0-\infty}$  and TMIC. For Cohort 5, a full PK profile is anticipated by the end of 6 hours; however, sampling out to 12 hours will provide additional information regarding the elimination tail. The above sampling scheme allows for a balance between the maximum coverage of the concentration profile across time required to adequately characterize the PK, while minimizing the number of blood samples per subject.

#### **4.2.3.2 Safety Endpoints**

Safety will be assessed through descriptive statistics within the safety analysis population for each age cohort. Safety assessments will include AEs, local tolerability assessments, clinical laboratory evaluations, vital sign measurements, and physical examinations.

### **4.3 Benefit/Risk**

In this trial, subjects will receive a single IV infusion of IMI/REL in addition to standard-of-care treatment. No direct or immediate clinical benefit is anticipated from participation in this single-dose PK study. While no direct clinical benefit to participants is anticipated, the risks of administration of a single dose of IMI/REL are considered to be minimal. Imipenem/cilastatin 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 (see more in Section 4.1.4 – Imipenem/Cilastatin Clinical Experience in Pediatric Populations). Furthermore, there are no significant or excessive adverse effects observed among other clinical studies involving IMI/REL to date (see more in Section 4.1.2 – Preclinical and Clinical Trials and Section 4.1.3 – Ongoing Clinical Trials).

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. Although more frequent, the proposed study procedures described in Section 6.0 – Trial Flow Chart are generally standard procedures performed for the target patient population (eg, chemistry and hematology measurements). One study visit is scheduled 14 days after study drug infusion and therefore will occur generally when the subject is no longer expected to be hospitalized; this visit can be conducted in person at the study site or by telephone, and only a concomitant medication review and AE monitoring will be conducted.

The procedures required for this protocol are necessary to support thorough evaluation of the PK and safety profile of the study drug. A thorough assessment of PK and safety in this study will support determination of adequate and safe dosing for evaluation of efficacy of treatment in subsequent confirmatory trial(s), thus ensuring an ethically sound treatment regimen that will minimize potential for treatment failure in this vulnerable population. As such, data from this study present a future opportunity to support availability of IMI/REL to pediatric patients with unmet medical need.

Notably, subjects are required to be concomitantly receiving or to have recently completed (within 48 hours prior to study drug administration) standard-of-care antibacterial treatment for their confirmed or suspected underlying infection. No reliance is placed on the single dose of IMI/REL to provide efficacious treatment.

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

## **5.0 METHODOLOGY**

### **5.1 Entry Criteria**

#### **5.1.1 Diagnosis/Condition for Entry into the Trial**

Male and female subjects from birth to <18 years of age with confirmed or suspected Gram-negative bacterial infection will be enrolled in this trial.

### **5.1.2 Subject Inclusion Criteria**

In order to be eligible for participation in this trial, the subject must:

1. Have a parent or LAR who provides written informed consent for the trial on the subject's behalf after understanding the study procedures, alternative treatments available, and risks involved with the study, and voluntarily agrees to allow the subject to participate. Assent is to be obtained from minors as applicable according to institutional practices.
2. Be able to comply with the protocol for the duration of the study.
3. Be male or female from birth to <18 years of age at screening.
4. For Cohorts 4 and 5, is at least 37 weeks postmenstrual age at the time of screening. Postmenstrual age is calculated by adding the gestational age at the time of birth to the chronological age at the time of screening.
5. Be hospitalized, currently receiving antibacterial treatment for confirmed or suspected Gram-negative bacterial infection, and expected to require hospitalization until at least 24 hours after completion of study drug administration. Subjects who are not receiving antibacterial treatment for the qualifying infection at the time of screening are eligible for this trial if either (1) they will be initiating antibacterial treatment for the qualifying infection prior to study drug administration, or (2) they have recently (within 48 hours prior to study drug administration) completed antibacterial treatment for the qualifying infection.
6. Meet 1 of the following categories:
  - a) The subject is a male who is not of reproductive potential, defined as a male who has azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).
  - b) The subject is a female who is not of reproductive potential, defined as a female who either: (1) who has not undergone menarche, (2) has had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion at least 6 weeks prior to screening, OR (3) has a congenital or acquired condition that prevents childbearing.
  - c) The subject is a female or a male who is of reproductive potential and agrees to avoid becoming pregnant or impregnating a partner from the time of consent through 24 hours after completion of study drug administration by complying with 1 of the following: (1) practice abstinence from heterosexual activity OR (2) use (or have their partner use) acceptable contraception during heterosexual activity. Acceptable methods of contraception are:

Single method (1 of the following is acceptable):

    - Intrauterine device
    - Vasectomy of a female subject's male partner
    - Contraceptive rod implanted into the skin

Combination method (requires use of 2 of the following):

- Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- Cervical cap with spermicide (nulliparous women only)
- Contraceptive sponge (nulliparous women only)
- Male condom or female condom (cannot be used together)
- Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and Ethical Review Committee (ERCs)/Institutional Review Boards (IRBs). Periodic abstinence (eg, calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

7. Have clinically stable renal function at the time of screening that is judged to be within acceptable ranges for age, as measured by creatinine clearance and as defined in Section 12.3.
8. Have sufficient intravascular access to receive study drug through an existing peripheral or central line.

### **5.1.3 Subject Exclusion Criteria**

The subject must be excluded from participating in the trial if the subject:

1. Has a personal history of hypersensitivity to IMI or to any of the following:
  - Any carbapenem, cephalosporin, penicillin, or other  $\beta$ -lactam agent
  - Other BLIs (eg, tazobactam, sulbactam, clavulanic acid, avibactam)
2. If female, is currently pregnant or breast feeding or has a positive serum  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG) pregnancy test prior to administration of the study drug.
3. Has a history of a seizure disorder (requiring ongoing treatment with anti-convulsive therapy or prior treatment with anti-convulsive therapy within the last 3 years).
4. Has used or plans to use valproic acid or divalproex sodium within 2 weeks prior to screening or at any point between screening and 24 hours after the completion of study drug infusion.

5. Has received treatment or plans to receive treatment with any carbapenem antibiotic within 48 hours prior to initiation of study drug infusion or at any point between administration of study drug and the last PK sample collection.
6. Has used or plans to use any of the following medications, which are organic anion transporter (OAT) 1 or OAT3 inhibitors, within 1 week prior to screening or at any point between screening and the last PK sample collection: cimetidine, probenecid, indomethacin, mefenamic acid, furosemide or other loop diuretics (eg, bumetanide, torsemide, ethacrynic acid), angiotensin receptor blockers (eg, valsartan), and ketorolac.
7. Is currently participating in or has participated in an interventional clinical trial with an investigational compound or device within 30 days prior to screening.
8. Has enrolled previously in the current trial and been discontinued, or has received REL for any other reason.
9. Has a current diagnosis of cystic fibrosis, meningitis, or severe sepsis.
10. Has a history or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might expose the subject to risk by participating in the trial, confound the results of the trial, or interfere with the subject's participation for the full duration of the trial.
11. Is expected to survive less than 72 hours after completion of study drug administration.
12. Has any of the following laboratory abnormalities at the time of screening (with the exception of values, as determined by the investigator, that would be part of normal physiologic process for a particular age group [eg, physiologic hyperbilirubinemia in a newborn]):
  - ALT or AST  $\geq 3 \times$  ULN,
  - ALT or AST  $\geq 2 \times$  ULN accompanied by total bilirubin  $>$ ULN,
  - Total bilirubin  $\geq 2 \times$  ULN, or
  - Any other clinically significant abnormal laboratory test results not related to the underlying infection, as determined by the investigator.
13. Has a history of clinically significant renal, hepatic, or hemodynamic instability (defined as a requirement for pharmacological intervention to manage blood pressure in the 24-hour window prior to enrollment).
14. Has planned use of cardiopulmonary bypass, extracorporeal membrane oxygenation, hemodialysis, or peritoneal dialysis during the study.
15. For Cohorts 1 through 3 only: Has weight outside of the 5th to 95th percentile based on age.
16. Is, at the time of signing informed consent, a user of recreational or illicit drugs or has had a recent history (within the last year) of drug or alcohol abuse or dependence.

17. Has a planned blood transfusion within 24 hours of study drug administration or expected before the end of the PK sampling.
18. Has had significant blood loss ( $\geq 5\%$  of total blood volume) within 4 weeks before the screening visit. Total blood volume can be estimated as 80 mL/kg of body weight.
19. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

## 5.2 Trial Treatment(s)

The treatment to be used in this trial is outlined below in [Table 1](#).

Table 1 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen	Use
IMI/REL <sup>a</sup>	Varies based on age cohort ( <a href="#">Table 2</a> )  Maximum dosage: Single IV infusion of 500 mg IMI/ 250 mg REL	Single dose	IV <sup>b</sup>	Visit 2 (Study Day 1)	Experimental

Abbreviation: IMI/REL: imipenem/cilastatin/relebactam  
<sup>a</sup> IMI/REL will be provided as a fixed-dose combination in a single vial.  
<sup>b</sup> Infused over 30 ( $\pm 5$ ) minutes (initial infusion duration for Cohorts 1 through 3; see Section 5.2.1.2.1 for modifications for these age cohorts) or 60 ( $\pm 5$ ) minutes (initial infusion duration for Cohorts 4 and 5).

A single IV dose of IMI/REL will be administered to subjects any time after initiating standard-of-care treatment for a confirmed or suspected Gram-negative bacterial infection.

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 trial treatments in accordance with the protocol and any applicable laws and regulations.

### 5.2.1 Dose Selection/Modification

#### 5.2.1.1 Dose Selection (Preparation)

[Table 2](#) displays the proposed initial doses of the study drug for each age cohort. The proposed initial doses may be modified as described in Section 5.2.1.2 – Dose Modification. The dose modifications for Cohorts 1 through 4 that occurred as a result of the first interim review in these cohorts (ie, after 50% enrollment; see Section 8.7) are described in Section 5.2.1.2.1, along with the results of the second interim review (ie, following completion of enrollment in Cohorts 1 through 3) that led to the initial doses for Cohorts 4 and 5.

Table 2 Imipenem/Cilastatin/Relebactam (IMI/REL) Doses by Age Cohort

Age Cohort	Age Range	IMI/REL Proposed Initial Dose <sup>a</sup>
1 (n=6)	12 to <18 years	15/7.5 mg/kg over 30 min
2 (n=6)	6 to <12 years	15/7.5 mg/kg over 30 min
3 (n=6)	2 to <6 years	15/7.5 mg/kg over 30 min
4 (n=8)	3 months to <2 years <sup>b</sup>	10/5 mg/kg over 60 min <sup>c</sup>
5 (n=18)	Birth to <3 months <sup>d</sup>	10/5 mg/kg over 60 min <sup>c</sup>

Abbreviations: IMI/REL: imipenem/cilastatin/relebactam; TBD: to be determined

<sup>a</sup> The proposed initial doses may be modified based on interim data as described in Section 5.2.1.2 – Dose Modification. The dose modifications for Cohorts 1 through 4 that occurred as a result of the first interim review in these cohorts are described in Section 5.2.1.2.1. Single IV doses for all cohorts will not exceed the adult maximum dose of 500 mg IMI and 250 mg REL.

<sup>b</sup> At least 4 subjects in Cohort 4 will be <1 year of age.

<sup>c</sup> Initial doses of IMI/REL for subjects in Cohorts 4 and 5 were selected based on PK modeling and simulation analyses, after incorporating observed PK data from Cohorts 1 through 3 (Section 5.2.1.2.1). Initial doses for Cohorts 4 and 5 were communicated to sites via a Protocol Clarification Letter.

<sup>d</sup> Cohort 5 will be further subdivided into the following 3 age subcohorts:

- 4 weeks to <3 months of age; at least 6 subjects
- 1 to <4 weeks of age; at least 6 subjects
- <1 week of age; at least 6 subjects

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. Additional details for preparation and administration of study drug are provided in a separate Pharmacy Manual.

### 5.2.1.2 Dose Modification

The goal of this trial is to determine doses of IMI/REL for each pediatric age cohort that achieve similar therapeutic exposure parameters as seen in clinical trials in adults and have an acceptable safety profile. As such, all observed PK data will be entered into a rolling population PK model-based simulation. For each age cohort, the Sponsor will assess dose suitability during the planned interim reviews based on the observed PK and safety data from the first half of subjects enrolled into the cohort. The following parameters will be considered in determination of pediatric doses:

- Simulated population PK parameters for each age cohort approach the following values, as expected in adults:
  - Single-dose REL exposure of  $AUC_{0-\infty} \geq 37.5 \mu\text{M}\cdot\text{hr}$  (and  $\leq 200 \mu\text{M}\cdot\text{hr}$ ). Doses associated with this exposure have been established as being well tolerated in adults.
  - $\geq 30\%$  TMIC (within proposed dosing interval) for single-dose imipenem (and  $AUC_{0-\infty} \leq 250 \mu\text{M}\cdot\text{hr}$ ). Doses achieving these targets have been established as safe and efficacious in adults.

- Observed safety data demonstrates an acceptable safety profile, as defined by no life-threatening toxicities considered by the investigator to be related to study treatment. Life-threatening toxicities are defined as follows:
  - For laboratory AEs, a grade of 4 on the Division of Microbiology and Infectious Diseases pediatric toxicity scale [12].
  - For clinical AEs, events that are considered serious due to being life-threatening, as defined in Section 7.2.4 – Evaluating Adverse Events and as documented on the electronic case report form (eCRF).

Modified doses will not exceed the adult maximum of 500 mg IMI and 250 mg REL for a single IV dose, and dose modifications, if required, will be communicated to sites via Protocol Clarification Letters.

#### **5.2.1.2.1 Dose Modifications and Decisions After Interim Reviews**

At the time of this protocol amendment (-02), enrollment into Cohorts 1 through 4 has been completed. As planned, protocol-defined interim reviews of safety and PK data were completed for the first 50% of subjects in each age cohort. The dose modifications that were made as a result of the interim reviews are shown in [Figure 2](#). These dose modifications were communicated to sites via Protocol Clarification Letters and are based on the following considerations:

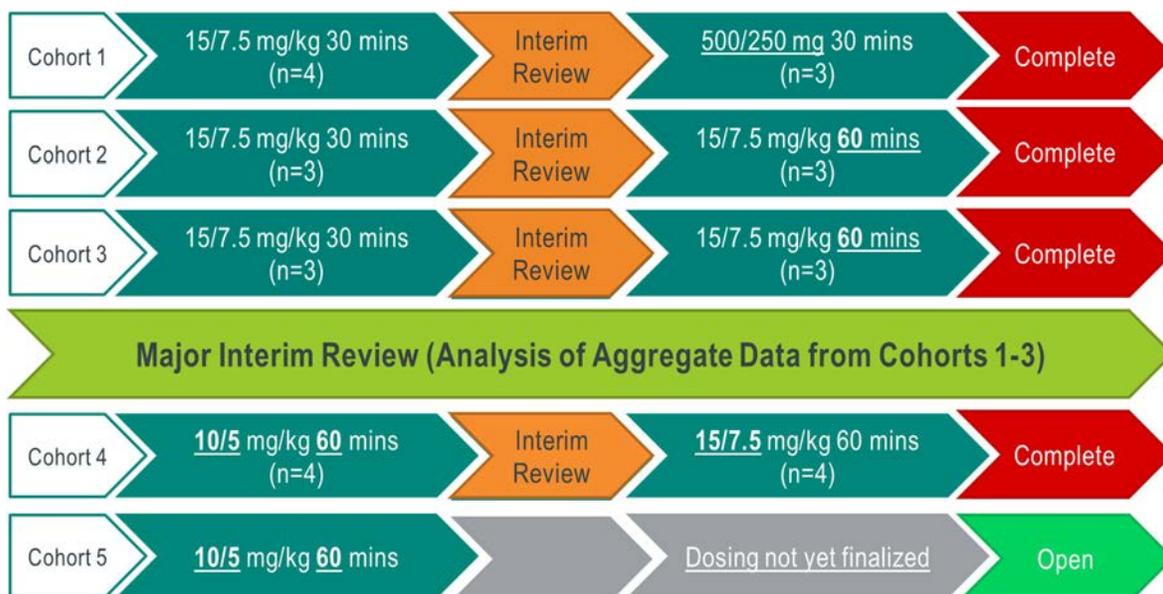
- At time of enrolling Cohorts 1 through 3, no pediatric-specific population PK model for imipenem and REL was available; therefore, PK endpoints from these cohorts were estimated based on an allometrically-scaled adult population PK model. The interim reviews in each cohort showed that the scaled adult model appropriately described the observed imipenem and REL concentrations from pediatric subjects in Cohorts 1 through 3.
- Cohort 1: At the initial dosing guidance of 15/7.5 mg/kg IMI/REL as a 30-minute IV infusion, all subjects received the full adult dose of 500/250 mg IMI/REL based on their weight. Based on modeling, likely weights of subjects in the age cohort would almost always necessitate the full 500/250 mg dose of IMI/REL; therefore, the dosing regimen was simplified to a flat single dose of 500/250 mg IMI/REL administered as a 30-minute IV infusion for the remaining subjects of Cohort 1.
- Cohort 2: Simulations showed that by increasing the study drug infusion duration from 30 minutes to 60 minutes at the proposed initial dose of 15/7.5 mg/kg IMI/REL, >90% of subjects in this age cohort would meet the protocol-defined safety targets, and ~ 75% of subjects in this age cohort would meet PK targets for both imipenem and REL. Therefore, the dosing regimen was changed to 15/7.5 mg/kg IMI/REL as a 60-minute intravenous infusion for the remaining Cohort 2 subjects in order to ensure the majority of patients met the safety and PK targets.
- Cohort 3: Simulations showed that by infusing IMI/REL at 15/7.5 mg/kg over 60 minutes (rather than over 30 minutes), ~98% of subjects in this age cohort would meet the protocol-defined safety targets for both imipenem and REL. Furthermore, a change in the infusion period from 30 minutes to 60 minutes was consistent with the

updated regimen for the remaining subjects in Cohort 2. Therefore, the dosing regimen was changed to 15/7.5 mg/kg IMI/REL as a 60-minute intravenous infusion for the remaining Cohort 3 subjects.

After completion of enrollment of Cohorts 1 through 3 (2 to <18 years of age), the protocol-defined interim review of aggregate safety and PK data from these 3 cohorts was conducted. The observed safety data for all 19 subjects who received IMI/REL demonstrated an acceptable safety profile. PK data from the 18 PK evaluable subjects were used to develop a pediatric-specific population PK model for imipenem and relebactam. In order to extrapolate the developed pediatric population PK model for the older cohorts (2 to <18 years of age) to Cohorts 4 and 5 (<2 years of age), an adjustment function was included to account for a lack of full renal maturation for the subjects in this age range. Simulations were conducted to project the initial doses for Cohorts 4 and 5. The dosing regimen specified in Table 2 for Cohorts 4 and 5 was selected based on drug exposures that were projected to provide optimal probability of safety and efficacy.

For Cohort 4, simulations from the interim review showed that infusing IMI/REL at 15/7.5 mg/kg (rather than 10/5 mg/kg) over 60 minutes would result in projected efficacy and safety targets similar to the evaluated initial Cohort 4 dose of 10/5 mg/kg. Furthermore, choosing a 15/7.5 mg/kg dose for the remaining 4 subjects enabled data collection over an expanded dosing range, and therefore supports population PK model optimization and future clinical use. Additionally, the 15/7.5 mg/kg dosing regimen of IMI/REL is consistent with the current PRIMAXIN®/TIENAM® (imipenem/cilastatin) dosing recommendations for pediatric patients, for which there is a long history of safe and efficacious use.

Figure 2 Dose Modifications for Cohorts 1, 2, 3, and 4 After Interim Reviews



### **5.2.2 Timing of Dose Administration**

A single dose of IMI/REL will be administered as an IV infusion. The infusion durations for each age cohort are as follows:

- Cohorts 1 through 3: subjects enrolled prior to the 50% interim review for each of these cohorts received a 30 ( $\pm 5$ )-minute infusion. Following the interim review (see Section 5.2.1.2.1), subjects in these cohorts received a 60 ( $\pm 5$ )-minute infusion.
- Cohort 4: subjects enrolled prior to the 50% interim review received a 60 ( $\pm 5$ )-minute infusion. Following the interim review (see Section 5.2.1.2.1), remaining subjects in this cohort also received a 60 ( $\pm 5$ )-minute infusion.
- Cohort 5: 60 ( $\pm 5$ ) minutes. Any modification to this infusion duration following the planned interim reviews will be communicated via a Protocol Clarification Letter.

The dose can be administered any time after initiating standard-of-care treatment for a confirmed or suspected Gram-negative bacterial infection, but no more than 48 hours following the screening visit for this study and no more than 48 hours after completing antibacterial treatment for the qualifying infection. The study drug must not be administered simultaneously through the same infusion line/lumen with any other drugs (including IV nonstudy drugs). If another IV drug is required either prior to or after study drug and only 1 line/lumen is available, an appropriate volume of saline flush must be used between IV infusions.

### **5.2.3 Trial Blinding**

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

## **5.3 Randomization or Treatment Allocation**

During the course of the study, subjects will be allocated to age cohorts by nonrandom assignment. After the informed consent form is signed by the parent or LAR and study eligibility is confirmed, designated site study staff will obtain the subject's treatment/randomization number from a computer-generated code via interactive voice or web response system (IVRS or IWRS).

## **5.4 Stratification**

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

1. Age: subjects will be allocated to age cohorts as described in Section 2.1 – Trial Design.

## **5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)**

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may

be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject's legally acceptable representative.

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

1. Valproic acid or divalproex sodium within 2 weeks prior to screening or at any point between screening and 24 hours after the completion of study drug infusion.
2. Any carbapenem antibiotic within 48 hours prior to initiation of study drug infusion or at any point between administration of study drug and the last PK sample collection.
3. Has used or plans to use any of the following medications, which are OAT1 or OAT3 inhibitors, within 1 week prior to screening or at any point between screening and the last PK sample collection: cimetidine, probenecid, indomethacin, mefenamic acid, furosemide or other loop diuretics (eg, bumetanide, torsemide, ethacrynic acid), angiotensin receptor blockers (eg, valsartan), and ketorolac.

## **5.6 Rescue Medications & Supportive Care**

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

## **5.7 Diet/Activity/Other Considerations**

Subjects will refrain from consumption of alcohol from screening through 24 hours after the completion of study drug infusion.

Subjects will avoid strenuous physical activity (eg, weight lifting, running, bicycling) from screening through 24 hours after the completion of study drug infusion.

## **5.8 Subject Withdrawal/Discontinuation Criteria**

### **5.8.1 Discontinuation of Treatment**

Discontinuation of treatment (for this single-dose study, this would be discontinuation of study drug partway through the infusion) does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment will still continue to participate in the trial as specified in Section 6.0 – Trial Flow Chart and Section 7.1.5.3 – Discontinued Subjects Continuing to be Monitored in the Trial.

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

Specific details regarding procedures to be performed at treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from treatment but continue to be monitored in the trial for any of the following reasons:

- The subject or subject’s legally acceptable representative requests to discontinue treatment.
- The subject has a medical condition or personal circumstance that, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk from continued administration of study drug.

For subjects who are discontinued from treatment but continue to be monitored in the trial, see Section 6.0 – Trial Flow Chart, and Section 7.1.5.3 – Discontinued Subjects Continuing to be Monitored in the Trial for those procedures to be completed at each specified visit.

Discontinuation from treatment is “permanent.” Once a subject is discontinued, he/she shall not be allowed to restart treatment.

### **5.8.2 Withdrawal from the Trial**

Subjects may withdraw from the trial at any time for any reason. If a subject withdraws from the trial, they will no longer receive treatment or be followed at scheduled protocol visits.

A subject must be withdrawn from the trial if:

- The subject or subject’s legally acceptable representative withdraws consent from the trial.
- The subject is lost to follow-up.

Specific details regarding procedures to be performed at the time of withdrawal from the trial are outlined in Section 7.1.4 – Other Procedures.

### **5.9 Subject Replacement Strategy**

If a subject discontinues from trial treatment, withdraws from the trial, or is missing PK samples, a replacement subject may be enrolled if deemed appropriate by the Sponsor in order to ensure that a sufficient number of evaluable PK samples are collected in each age cohort.

The replacement subject will be assigned a unique treatment/randomization number by the IVRS or IWRS. The subject being replaced will still be included in the safety analysis if they received any study treatment.

### **5.10 Beginning and End of the Trial**

The overall trial begins when the first subject signs the informed consent/assent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, withdraws from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

### **5.11 Clinical Criteria for Early Trial Termination**

The clinical trial may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable. In addition, further recruitment in the trial or at (a) particular trial site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

## 6.0 TRIAL FLOW CHART

Trial Period:	Screening	Treatment	Post-treatment		Early Discontinuation <sup>1</sup>
Visit Title:	1 Screening	2	3	4	Unscheduled
Scheduled Day:	-2 to 1 <sup>2</sup>	1	2	15 (In Person or by Telephone)	Unscheduled
Scheduling Window:			24 (±8) hours after completion of study drug infusion	+2 days	Discontinuation
<b>Administrative Procedures</b>					
Informed Consent/Assent <sup>3</sup>	X				
Inclusion/Exclusion Criteria	X				
Subject Identification Card	X				
Medical History	X				
Prior and Concomitant Medication Review <sup>4</sup>	X	X	X	X	X
IMI/REL (Study Drug) Administration		X			
<b>Clinical Procedures/Assessments</b>					
Full Physical Examination	X				
Directed Physical Examination		X <sup>5</sup>	X		X
Height	X				
Weight	X				
Vital Sign Measurements (heart rate, blood pressure, respiratory rate, temperature)	X	X <sup>6</sup>	X		X
Adverse Events Monitoring	X	X	X	X	X
Local Tolerability Monitoring		X	X		X <sup>7</sup>
<b>Laboratory Procedures/Assessments</b>					
Serum Pregnancy Test (if applicable) <sup>8</sup>	X				
Hematology Sampling <sup>9</sup>	X		X		X
Blood Chemistry Sampling <sup>9</sup>	X		X		X
Urinalysis Sampling <sup>10</sup>	X		X		X
Plasma Pharmacokinetic Sampling <sup>11</sup>		X <sup>12</sup>			

- 
1. To be performed for all subjects who discontinue from treatment (ie, discontinue study drug partway through the infusion) or withdraw from the trial at any point after the start of study drug infusion.
  2. Screening procedures must be completed within 48 hours prior to the start of study drug infusion.
  3. Written informed consent from parent or legally acceptable representative and age-appropriate assent.
  4. Includes medications of mothers of breast-fed subjects.
  5. To be performed before the start of study drug infusion.
  6. To be performed (1) within 2 hours before the start of study drug infusion, (2) 15 to 30 minutes after completion of study drug infusion, and (3) 4.5 to 6 hours after the start of study drug infusion.
  7. Only for subjects who discontinue from treatment or withdraw from the trial at any point between the start of study drug infusion and the Day 2 visit.
  8. Female subjects of child-bearing potential only.
  9. If blood tests (chemistry and hematology) have been conducted at the local laboratory within 48 hours of dosing, they may be used (ie, they do not need to be repeated at screening for the purpose of the study).
  10. Urine will be collected from subjects who are either toilet trained and able to provide a specimen, catheterized, or fitted with a urine collection bag.
  11. The method of collection for pharmacokinetic 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.
  12. Blood samples for plasma pharmacokinetic assessments will be collected at the following time points: (1) within 30 minutes before the start of study drug infusion, (2) within 10 minutes after the end of study drug infusion, (3) 1.5 to 2.5 hours (for Cohorts 1 through 4) or 2 to 5 hours (for Cohort 5) after the start of study drug infusion, and (4) 4.5 to 6 hours (for Cohorts 1 through 4) or 6 to 12 hours (for Cohort 5) after the start of study drug infusion.

## **7.0 TRIAL PROCEDURES**

### **7.1 Trial Procedures**

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent, and assent if applicable, be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

#### **7.1.1 Administrative Procedures**

##### **7.1.1.1 Informed Consent/Assent**

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent, and assent if applicable, from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate consent/assent is in place.

###### **7.1.1.1.1 General Informed Consent/Assent**

Consent/assent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent/assent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent/assent form should be given to the subject before participation in the trial.

The initial informed consent/assent form, any subsequent revised written informed consent/assent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. 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 subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent/assent form template at the protocol level. The assent, as applicable, will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

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

#### **7.1.1.2 Inclusion/Exclusion Criteria**

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

#### **7.1.1.3 Subject Identification Card**

All subjects and/or subjects' parents or legally acceptable representative (as appropriate) will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent/assent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

#### **7.1.1.4 Medical History**

Relevant medical history will be obtained by the investigator or qualified designee. Details of the qualifying infection will be recorded.

#### **7.1.1.5 Prior and Concomitant Medications Review**

##### **7.1.1.5.1 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 subject within 7 days before screening. For breast-fed subjects, medications taken by the mother during the same timeframe will also be recorded.

##### **7.1.1.5.2 Concomitant Medications**

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. For breast-fed subjects, medications taken by the mother during the trial will also be recorded.

#### **7.1.1.6 Assignment of Screening Number**

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1 – Screening.

#### **7.1.1.7 Assignment of Treatment/Randomization Number**

All eligible subjects will be allocated, by non-random assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 treatment/randomization number.

#### **7.1.1.8 Trial Compliance**

Interruptions from the protocol specified treatment require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of the single dose of trial medication will be witnessed by the investigator and/or trial staff, and the time and date will be recorded in the subject's eCRF.

### **7.1.2 Clinical Procedures/Assessments**

#### **7.1.2.1 Full and Directed Physical Examinations**

All physical examinations must be performed by an investigator or medically qualified designee (consistent with local requirements).

A complete physical examination performed at the screening visit includes the following assessments: general appearance, head, eyes, ears/nose/throat, neck, lymph nodes, skin, lungs, heart, abdomen, musculoskeletal, and neurologic evaluations. Rectal and genitourinary/pelvic exams should be performed when clinically indicated. If a physical examination was performed within 72 hours prior to screening, those results can be recorded and a repeat physical examination is not required.

After the initial full physical examination, a directed physical examination targeted to the subject's illness and complaints will be performed at subsequent visits as specified in Section 6.0 – Trial Flow Chart.

Any abnormal or clinically significant findings from the physical examinations must be recorded on the appropriate eCRF.

#### **7.1.2.2 Height and Weight**

The subject's height and weight should be measured at screening.

### **7.1.2.3 Vital Sign Measurements**

Vital sign measurements should include heart rate, blood pressure, respiratory rate, and oral temperature. Subjects should be in a seated or semirecumbent position prior to having vital sign measurements obtained. For those subjects who cannot sit up for any reason (eg, neonates, infants, intubated subjects), vital sign measurements will be taken in a supine or semirecumbent position. Oral temperatures should be taken, but if oral is not possible, tympanic, rectal, or axillary methods are acceptable.

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

### **7.1.2.4 Adverse Event Monitoring**

Please refer to Section 7.2 – Assessing and Recording Adverse Events for details regarding assessment and documentation of AEs. Laboratory AEs will be based on safety laboratory test results, including hematology and chemistry tests from blood and urinalysis from urine. All AEs should be documented on the appropriate eCRF. Refer to Section 7.1.3 – Laboratory Procedures/Assessments and Section 6.0 – Trial Flow Chart for more details on types of tests and timing of collection.

### **7.1.2.5 Local Tolerability Monitoring**

Local infusion site tolerability will be evaluated at the time points specified in Section 6.0 – Trial Flow Chart. The tolerability of all study therapy at the local IV infusion site will be based on investigator inspection and, when applicable, subject comments regarding signs and symptoms of intolerance. The IV infusion site should be observed to determine the presence/absence of erythema, induration, pain, tenderness, warmth, swelling, ulceration, local phlebitis, rash, or other reactions.

### **7.1.3 Laboratory Procedures/Assessments**

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood to be drawn over the course of the trial (from pre-trial to post-trial visits), including approximate blood volumes drawn by visit and by sample type per subject, can be found in Appendix 12.2 – Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types.

#### **7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry, and Urinalysis)**

Laboratory tests for hematology, chemistry and urinalysis are specified in [Table 3](#).

Clinically stable renal function, as measured by creatinine clearance (see Appendix 12.3), is an inclusion criterion for this trial. In addition to values obtained from scheduled chemistry blood draws during the study, the serum creatinine values used to calculate creatinine clearance for eligibility determination will also be recorded on the appropriate eCRF.

Urine will be collected from subjects who are either toilet trained and able to provide a specimen, catheterized, or fitted with a urine collection bag.

Table 3 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum $\beta$ -hCG <sup>a</sup>
Hemoglobin	Alkaline phosphatase	Glucose	
Platelet count	ALT	Protein	
WBC count (total and differential)	AST	Specific gravity	
Neutrophils (% absolute)	Bicarbonate	Microscopic exam, if abnormal results are noted	
Band neutrophils (% absolute)	Calcium	pH	
Lymphocytes (% absolute)	Carbon dioxide		
Eosinophils (% absolute)	Chloride		
Basophils (%)	Creatinine		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Total bilirubin		
	Direct and indirect bilirubin, if total bilirubin is elevated above the ULN		
	Total protein		
	Blood urea nitrogen		

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase;  $\beta$ -hCG:  $\beta$ -human chorionic gonadotropin; ULN: upper limit of normal; WBC: white blood cell.

a. Female subjects of child-bearing potential only.

### 7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

Four PK samples per subject will be collected in each of the age cohorts as follows:

1. First PK sample: predose sample taken within 30 minutes before the start of study drug infusion.
2. Second PK sample: collected within 10 minutes after the end of study drug infusion.
3. Third PK sample:
  - Cohorts 1 through 4: obtained 1.5 to 2.5 hours after the start of study drug infusion.
  - Cohort 5: obtained 2 to 5 hours after the start of study drug infusion.

4. Fourth PK sample:

- Cohorts 1 through 4: obtained 4.5 to 6 hours after the start of study drug infusion.
- Cohort 5: obtained 6 to 12 hours after the start of study drug infusion.

All PK samples must be drawn within the specified time windows, and the actual sampling times must be documented. This sampling scheme allows for a balance between the maximum coverage of the concentration profile across time required to adequately characterize the PK profile, while maintaining a minimal number of samples per subject.

The following model-based and derived PK parameters will be calculated for REL and/or imipenem, as appropriate:

- $AUC_{0-\infty}$
- $C_{max}$
- %TMIC (imipenem only)
- Systemic clearance (CL)
- Central volume of distribution ( $V_c$ )

The following noncompartmental analysis (NCA)-based PK parameters will be calculated for cilastatin:

- $AUC_{0-\infty}$
- Time to maximum observed plasma drug concentration
- Concentration at end of infusion (CEOI)
- $t_{1/2}$
- CL
- Volume of distribution ( $V_{ss}$ )

#### **7.1.3.2.1 Blood Collection for Plasma MK-7655A**

Sample collection, storage, and shipment instructions for plasma samples will be provided in the operations/laboratory manual.

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.

## **7.1.4 Other Procedures**

### **7.1.4.1 Withdrawal/Discontinuation**

Subjects who discontinue treatment prior to completion of the treatment regimen (ie, discontinuation of study drug partway through the infusion) should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the early withdrawal trial visit, as specified in Section 6.0 – Trial Flow Chart, should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

### **7.1.4.2 Subject Blinding/Unblinding**

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

### **7.1.4.3 Domiciling**

In order to participate in this study, subjects must be hospitalized and expected to remain hospitalized until at least 24 hours after completion of study drug administration.

### **7.1.4.4 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 is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

## **7.1.5 Visit Requirements**

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

### **7.1.5.1 Screening**

Within 48 hours prior to the start of study drug infusion, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1 – Entry Criteria. Screening procedures may be repeated after consultation with the Sponsor. If the subject is rescreened, screening procedures should be repeated, unless they fall within the window specified.

### **7.1.5.2 Treatment Period**

Details regarding procedures, assessments, and scheduling windows for the single treatment visit (ie, Visit 2) are presented in Section 6.0 – Trial Flow Chart. Notably, blood samples for plasma PK assessments and vital sign measurements will be collected several times at Visit 2 (see Section 6.0 – Trial Flow Chart for further details).

### **7.1.5.3 Discontinued Subjects Continuing to be Monitored in the Trial**

Subjects that discontinue treatment (ie, subjects that discontinue from study drug partway through the infusion) or who withdraw from the trial at any point after the start of study drug infusion 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 subjects who discontinue from treatment or withdraw from the trial between the start of study drug infusion and the Day 2 visit) completed as per Section 6.0 – Trial Flow Chart, but do not need to have PK sampling performed.

Subjects that withdraw from the trial prior to receiving a dose of study drug (eg, due to removal of consent by the parent or LAR, or due to an emergent condition or circumstance which, in the opinion of the investigator or Sponsor, places the subject at unnecessary risk through continued participation, or does not allow adherence to the protocol) do not need to undergo further visits or assessments.

### **7.1.5.4 Post-Trial**

Subjects will be required to either return to the study site or have a telephone contact approximately 14 days after the single dose of study drug for a concomitant medication review and AE monitoring.

## **7.2 Assessing and Recording Adverse Events**

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. 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.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo

or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 14 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the Electronic Data Capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

### **7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor**

In this trial, an overdose is any dose higher than 10% of the calculated age-appropriate dose specified in Section 5.2.1.1 – Dose Selection (Preparation) or in subsequent Protocol Clarification Letters.

If an adverse event(s) is associated with (“results from”) the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a non-serious adverse event, unless other serious criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious adverse event, using the terminology “accidental or intentional overdose without adverse effect.”

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

### **7.2.2 Reporting of Pregnancy and Lactation to the Sponsor**

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be

excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 14 days following cessation of Sponsor's product must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of 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.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

### **7.2.3 Immediate Reporting of Adverse Events to the Sponsor**

#### **7.2.3.1 Serious Adverse Events**

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

**Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements.

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

Refer to [Table 4](#) for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

### **7.2.3.2 Events of Clinical Interest**

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.\*

\*Note: These criteria are based upon 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 trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial 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  $5 \times$  ULN as a result of within-protocol-specific testing or unscheduled testing.

### **7.2.4 Evaluating Adverse Events**

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in [Table 4](#). The investigator's assessment of causality is required for each adverse event. Refer to [Table 4](#) for instructions in evaluating adverse events.

Table 4 Evaluating Adverse Events

<b>Maximum Intensity</b>	<b>Mild</b>	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	<b>Moderate</b>	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	<b>Severe</b>	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
<b>Seriousness</b>	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	† <b>Results in death</b> ; or	
	† <b>Is life threatening</b> ; or places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	† <b>Results in a persistent or significant disability/incapacity</b> (substantial disruption of one's ability to conduct normal life functions); or	
	† <b>Results in or prolongs an existing inpatient hospitalization</b> (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 pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	† <b>Is a congenital anomaly/birth defect</b> (in offspring of subject taking the product regardless of time to diagnosis); or	
	<b>Is a cancer</b> (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); <b>or</b>	
	Overdose, although not serious per ICH definition, whether accidental or intentional, with or without an accompanying adverse event/serious adverse event, is reportable to the Sponsor within 24 hours to meet certain local requirements.	
<b>Other important medical events</b> that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).		
<b>Duration</b>	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
<b>Action taken</b>	Did the adverse event cause the Sponsor's product to be discontinued?	
<b>Relationship to Sponsor's Product</b>	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event 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 done. 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 drug and the adverse event based upon the available information	
	<b>The following components are to be used to assess the relationship between the Sponsor's product and the AE</b> ; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:	
	<b>Exposure</b>	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	<b>Time Course</b>	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
<b>Likely Cause</b>	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors	

<b>Relationship to Sponsor's Product (continued)</b>	<b>The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)</b>	
	<b>Dechallenge</b>	Was the Sponsor's product 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 Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	<b>Rechallenge</b>	Was the subject re-exposed to the Sponsor's product in this trial? 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 trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	<b>Consistency with Trial Treatment Profile</b>	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product 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 his/her best clinical judgment, including consideration of the above elements.		
<b>Record one of the following:</b>	<b>Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).</b>	
<b>Yes, there is a reasonable possibility of Sponsor's product relationship.</b>	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
<b>No, there is not a reasonable possibility of Sponsor's product relationship</b>	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

### 7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

## 8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any final database lock, changes are made to primary and/or key secondary objectives, or the related statistical methods, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental Statistical Analysis Plan and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan will be issued for this study.

### 8.1 Statistical Analysis Plan Summary

Key elements of the Statistical Analysis Plan are summarized below; the comprehensive plan is provided in Section 8.2 – Responsibility for Analyses/In-House Blinding through Section 8.9 – Sample Size and Power Calculations.

<b>Study Design Overview</b>	A Phase 1b, Open-label, Single-dose Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of MK-7655A in Pediatric Subjects From Birth to Less Than 18 Years of Age With Confirmed or Suspected Gram-negative Infections
<b>Treatment Assignment</b>	Single IV dose of MK-7655A (IMI/REL)
<b>Analysis Populations</b>	<b>Pharmacokinetics:</b> Per Protocol: all subjects who comply with the protocol sufficiently to ensure that their data will be likely to exhibit the primary endpoints, according to the underlying scientific model, and who have at least 1 postdose PK data point. <b>Safety:</b> All Subjects as Treated (ASaT): All subjects who received infusion (including partial doses) of study medication.
<b>Primary Endpoint(s)</b>	<b>Pharmacokinetic:</b> Plasma PK concentration data; 4 PK samples per subject will be collected. Primary model-based endpoints for REL and imipenem and non-model-based endpoints for cilastatin are listed in Section 8.4.1 – Pharmacokinetic/Pharmacodynamic Endpoints.
<b>Secondary Endpoints</b>	<b>Safety:</b> Safety evaluation will be based on the following endpoints: AEs (including ECIs), local tolerability assessments, clinical laboratory data, vital sign measurements, and physical examinations findings.

<p><b>Modeling and Simulation (M&amp;S) Methods for Key Pharmacokinetic Analyses</b></p>	<p>Pediatric REL and imipenem data will be used to determine pediatric PK parameters by using the previous adult PK model as a starting point. The PK parameters will be continuously updated as pediatric PK data become available from each age cohort. A nonlinear mixed effects modeling approach will be applied for model building.</p> <p>The target is <math>AUC_{0-\infty} \geq 37.5 \mu\text{M}\cdot\text{hr}</math> (and <math>\leq 200 \mu\text{M}\cdot\text{hr}</math>) for REL and <math>TMIC \geq 30\%</math> (and <math>AUC_{0-\infty} \leq 250 \mu\text{M}\cdot\text{hr}</math>) for imipenem. The goal of model-based simulations will be to derive a dosing regimen where these predefined targets are jointly achieved in a proportion of pediatric subjects similarly covered in adults (~90% probability of target attainment) for each age cohort.</p> <p>For cilastatin, descriptive statistics will be provided for PK parameters by age cohort, based on NCA.</p> <p>Details on modeling and simulation (M&amp;S) methods are provided in Section 8.6.1 – Modeling &amp; Simulation Methods for Pharmacokinetic Analyses.</p>
<p><b>Statistical Methods for Safety Analyses</b></p>	<p>Descriptive statistics will be provided for all safety assessments described above.</p>
<p><b>Interim Reviews</b></p>	<p>Interim reviews of PK and safety data are planned at 3 stages in the study. Dose modification may be suggested based on interim review results. The planned interim reviews are summarized in Section 8.7 – Interim Review for Potential Dose Adjustment.</p>
<p><b>Multiplicity</b></p>	<p>No multiplicity adjustment is planned.</p>
<p><b>Sample Size and Power</b></p>	<p><b>Based on PK Precision</b>                  Proposed number of study participants by pediatric subset:  <b>Cohort 1</b> (age 12 to &lt;18 years); at least 6 subjects  <b>Cohort 2</b> (6 to &lt;12 years); at least 6 subjects  <b>Cohort 3</b> (2 to &lt;6 years); at least 6 subjects  <b>Cohort 4</b> (3 months to &lt;2 years); at least 8 subjects, at least 4 of whom are &lt;1 year of age  <b>Cohort 5</b> (birth to &lt;3 months); at least 18 subjects with at least 6 younger neonates (&lt;1 week age), at least 6 older neonates (1 to &lt;4 weeks age), and at least 6 infants (4 weeks to &lt;3 months)</p> <p>Details on sample size calculation are provided in Section 8.9 – Sample Size and Power Calculations.</p>

## 8.2 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. The analyses and summaries described in Section 8.6.1 – Modeling & Simulation Methods for Pharmacokinetic Analyses are the responsibility of the Quantitative Pharmacology and Pharmacometrics group and the Early Clinical Development Statistics group of the Sponsor.

This trial is being conducted as a nonrandomized, open-label study (ie, subjects, investigators, and Sponsor personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned).

Subjects participating in this trial will be allocated to age cohorts as described in Section 2.1 – Trial Design. The Clinical Biostatistics department will generate the allocation schedule, and allocation/non-random assignment will be implemented in an IVRS or IWRS.

There are no plans to conduct formal interim analyses in this study. Planned interim reviews of PK and safety data for each age cohort are described in Section 8.7 – Interim Review for Potential Dose Adjustment. An internal M&S team will be appointed to review the PK profile and safety and tolerability data for each age cohort when PK data from 50% of subjects in each cohort is available. Dose modification may be suggested based on the results of interim reviews as described in Section 5.2.1.2 – Dose Modification.

### **8.3 Hypotheses/Estimation**

Objectives of the study are stated in Section 3.0 – Objective(s) and Hypothesis(es). No hypothesis testing will be performed for this study.

### **8.4 Analysis Endpoints**

#### **8.4.1 Pharmacokinetic/Pharmacodynamic Endpoints**

Plasma concentrations of REL, imipenem, and cilastatin will be determined. The REL and imipenem data will be used to develop a pediatric population PK model, which will be used to perform simulations to derive suitable pediatric doses. Cilastatin data will be used to summarize its PK profile based on NCA.

For REL, plasma exposure ( $AUC_{0-\infty}$ ) and  $C_{max}$  will be the primary endpoints. For imipenem, %TMIC, plasma exposure ( $AUC_{0-\infty}$ ), and  $C_{max}$  will be the primary endpoints. In addition, the following model-based population mean PK parameters for both REL and imipenem will be determined: CL and  $V_c$ .

For cilastatin, the following PK parameters will be determined:  $AUC_{0-\infty}$ ,  $C_{EOI}$ ,  $t_{1/2}$ , CL, and  $V_{ss}$ .

#### **8.4.2 Safety Endpoints**

A description of safety measures is contained in Section 7.0 – Trial Procedures. Safety assessments will include AEs, local tolerability assessments, clinical laboratory evaluations, vital sign measurements, and physical examinations.

### **8.5 Analysis Populations**

#### **8.5.1 Pharmacokinetics Population**

The Per Protocol population will be used for the PK analysis. This population is the set of data generated by the subset of subjects who comply with the protocol sufficiently to ensure that these data will be likely to exhibit the primary endpoints, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements, and absence of major protocol violations. Subjects with major protocol violations will be identified to the extent possible by individuals responsible for data

collection/compliance and its analysis and interpretation. Any subjects or data values excluded from analysis will be identified, along with their reasons for exclusion, in the CSR. At the end of the trial, all subjects who are compliant with the trial procedure as described and have at least 1 postdose PK data point available will be included in the primary PK analysis dataset.

### **8.5.2 Safety Analysis Populations**

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all allocated subjects who received infusion (including partial doses) of study medication.

## **8.6 Statistical Methods**

### **8.6.1 Modeling & Simulation Methods for Pharmacokinetic Analyses**

Relebactam and imipenem data will be used to develop a pediatric population PK model by using previous adult data in the form of the adult population PK model, which will be continuously updated as pediatric PK data become available from each age cohort. 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. A Modeling and Simulation Analysis Plan with further details on the methodology will be prepared and finalized before database lock and analysis of the data.

There will be no formal hypothesis testing. The target is  $AUC_{0-\infty} \geq 37.5 \mu\text{M}\cdot\text{hr}$  (and  $\leq 200 \mu\text{M}\cdot\text{hr}$ ) for REL and  $TMIC \geq 30\%$  (and  $AUC_{0-\infty} \leq 250 \mu\text{M}\cdot\text{hr}$ ) for imipenem. The goal of model-based simulations will be to derive a dosing regimen where these targets are jointly achieved in a proportion of pediatric subjects 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.

For cilastatin, an NCA will be conducted to determine its PK parameters. Descriptive statistics will be provided for cilastatin PK parameters by age cohort.

### **8.6.2 Statistical Methods for Safety Analyses**

Safety and tolerability will be assessed by clinical review of all relevant parameters including the incidence, severity, and type of AEs, changes in clinical laboratory tests, and changes from baseline in vital sign measurements at the interim reviews and the end of study.

The type and incidence of all AEs and serious adverse events (SAEs) will be tabulated for each age cohort and dose level. The broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, a drug-related AE, an SAE, a drug-related SAE, and who discontinued due to an AE, as well as the most frequently occurring individual AEs will be summarized in the same manner. Special attention will be given to local tolerability events occurring at time of study drug administration and to those subjects who discontinue due to

an AE or an SAE. Descriptive and/or summary statistics for the raw laboratory safety tests, vital sign measurements, and/or changes from baseline may also be computed, as deemed clinically appropriate.

## **8.7 Interim Reviews for Potential Dose Adjustment**

Interim reviews of PK and safety data will occur at 3 stages in the study. First, interim reviews were performed for each of Cohorts 1 through 3 in this study when data from 50% (3 subjects) of subjects were available from a specific cohort. Second, an interim review of complete aggregated PK data from Cohorts 1 through 3 was performed prior to enrollment of Cohorts 4 and 5. Third, interim reviews for each of Cohorts 4 and 5 will be performed when data from 50% of subjects are available from a specific cohort. Results will be reviewed by an internal team. During the first and third interim reviews, the suitability of the initial dose for each age cohort will be assessed and a dose modification may be suggested for the remaining 50% of subjects in that cohort, as described in Section 5.2.1.2 – Dose Modification. The dose modifications that occurred as a result of the completed interim reviews are described in Section 5.2.1.2.1.

## **8.8 Multiplicity**

Because there are no pre-specified hypotheses, no adjustments for multiplicity will be made.

## **8.9 Sample Size and Power Calculations**

The proposed number of study participants by pediatric subset includes the following:

- Cohort 1 (age 12 to <18 years); at least 6 subjects
- Cohort 2 (6 to <12 years); at least 6 subjects
- Cohort 3 (2 to <6 years); at least 6 subjects
- Cohort 4 (3 months to <2 years); at least 8 subjects, at least 4 of whom are <1 year of age
- Cohort 5 (birth to <3 months); at least 18 subjects with at least 6 younger neonates (<1 week age), at least 6 older neonates (1 to <4 weeks age), and at least 6 infants (4 weeks to <3 months)

A simulation-based methodology was implemented in order to determine the appropriate sample size for each pediatric age cohort that would have at least 80% probability to achieve reasonable precision, defined as the 95% confidence interval within 60% to 140% of the population mean (approximately  $\leq 20\%$  RSE [relative standard error]), in the model-based estimation of primary PK parameters for both REL and imipenem in each pediatric age cohort. Variability in primary PK parameters was assumed to be the same as that estimated in adults based on the adult population PK model (coefficient of variation (%CV) for imipenem: 50% for CL, 75% for  $V_c$ ; %CV for REL: 40% for CL, 50% for  $V_c$ ).

The proposed trial design, in terms of sample sizes combined with the PK sampling scheme, was found to be sufficient to have >80% probability (based on replicate simulations) to

achieve the defined target precision in model-based primary PK parameter estimates (CL, Vc) for both REL and imipenem, and thus, is expected to adequately capture the PK characterization for both drugs in the pediatric population.

## **9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES**

### **9.1 Investigational Product**

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 investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in [Table 5](#).

Clinical supplies will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies.

Table 5 Product Descriptions

<b>Product Name &amp; Potency</b>	<b>Dosage Form</b>	<b>Source/Additional Information</b>
MK-7655A, MK-7655 250 mg/ Imipenem 500 mg/ Cilastatin 500 mg	Powder for Constitution	Provided centrally by the Sponsor

### **9.2 Packaging and Labeling Information**

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Subjects will receive open-label, single-dose vials. No kitting is required.

### **9.3 Clinical Supplies Disclosure**

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Treatment MK-7655A, MK-7655 250 mg, IMIPENEM 500 mg and CILASTATIN EQUIVALENT 500 mg (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

### **9.4 Storage and Handling Requirements**

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

## **9.5 Discard/Destruction>Returns and Reconciliation**

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial 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.

## **9.6 Standard Policies**

Trial site personnel will have access to a central electronic treatment allocation/randomization system (IVRS/IWRS system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

## **10.0 ADMINISTRATIVE AND REGULATORY DETAILS**

### **10.1 Confidentiality**

#### **10.1.1 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 institutional review board, ethics review committee (IRB/ERC) 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 trial 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.

#### **10.1.2 Confidentiality of Subject Records**

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

### **10.1.3 Confidentiality of Investigator Information**

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

### **10.1.4 Confidentiality of IRB/IEC Information**

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. 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.

## **10.2 Compliance with Financial Disclosure Requirements**

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, commonly 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.

### **10.3 Compliance with Law, Audit and Debarment**

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

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

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial 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 as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or

contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

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

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

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the Protocol/CSR CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

#### **10.4 Compliance with Trial Registration and Results Posting Requirements**

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to <http://www.clinicaltrials.gov>,

www.clinicaltrialsregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial 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 trial or its results to those registries.

### **10.5 Quality Management System**

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

### **10.6 Data Management**

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

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

### **10.7 Publications**

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

## **11.0 LIST OF REFERENCES**

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## 12.0 APPENDICES

### 12.1 Merck Code of Conduct for Clinical Trials

**Merck\***  
**Code of Conduct for Clinical Trials**

#### **I. Introduction**

##### **A. Purpose**

Merck, 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 subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

##### **B. Scope**

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

#### **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 Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

###### **2. Site Selection**

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

###### **3. Site Monitoring/Scientific Integrity**

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

##### **B. Publication and Authorship**

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. 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 of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. 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. Merck funding of a trial will be acknowledged in publications.

### **III. Subject Protection**

#### **A. IRB/ERC review**

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

#### **B. Safety**

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects 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. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck 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**

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

#### **D. Genomic Research**

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

### **IV. Financial Considerations**

#### **A. Payments to Investigators**

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

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

#### **B. Clinical Research Funding**

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

#### **C. Funding for Travel and Other Requests**

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

### **V. Investigator Commitment**

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

\* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

## 12.2 Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types

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 (blood culture, hematology with differential, and clinical chemistry panels). With this recognition in mind, expected blood volumes for the youngest age group (neonates) are calculated below:

Trial Visit/Cycle/etc:	Screening Visits 1	Treatment Visit 2	Post-Treatment Visit 3	Post-Treatment Visit 4
<b>Blood Parameter</b>	<b>Approximate Blood Volume</b>			
Serum $\beta$ -Human Chorionic Gonadotropin ( $\beta$ -hCG) <sup>a</sup>	0.5 mL			
Hematology	0.5 mL		0.5 mL	0.5 mL
Blood Chemistry	0.5 mL		0.5 mL	0.5 mL
Plasma Pharmacokinetics		1 mL (4 $\times$ 250 $\mu$ L)		
Expected Total (mL)	1.5 mL	1 mL	1 mL	1 mL
a. For female subjects of child-bearing potential only.				

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 subjects in this study (ie, female neonates in the first percentile of growth according to World Health Organization growth charts). Maximum volume for an individual subject should be based on weight and should generally not exceed 3% of total blood volume (2.4 mL blood per kg of body weight) unless appropriate justification is documented by the investigator.

### 12.3 Acceptable Creatinine Clearance Ranges by Age Range for Study Inclusion

Age Range	Creatinine Clearance Acceptable Range for Inclusion <sup>a</sup>	Formula for Estimating Creatinine Clearance <sup>b</sup>
12 to <18 years	≥80 mL/min	Cockcroft-Gault <sup>c</sup>
2 to <12 years	≥80 mL/min/1.73m <sup>2</sup>	Modified Schwartz <sup>d</sup>
18 months to <2 years	≥76 mL/min/1.73m <sup>2</sup>	Modified Schwartz <sup>d</sup>
12 to <18 months	≥73 mL/min/1.73m <sup>2</sup>	Modified Schwartz <sup>d</sup>
8 to <12 months	≥65 mL/min/1.73m <sup>2</sup>	Modified Schwartz <sup>d</sup>
14 weeks to <8 months	≥57 mL/min/1.73m <sup>2</sup>	Modified Schwartz <sup>d</sup>
6 to <14 weeks	≥47 mL/min/1.73m <sup>2</sup>	Modified Schwartz <sup>d</sup>
2 to <6 weeks	≥41 mL/min/1.73m <sup>2</sup>	Modified Schwartz <sup>d</sup>
1 to <2 weeks	≥25 mL/min/1.73m <sup>2</sup>	Modified Schwartz <sup>d</sup>
Birth to <1 week	≥20 mL/min/1.73m <sup>2</sup>	Modified Schwartz <sup>d</sup>

a. Normal creatinine clearance ranges taken from published lower-bound standard deviation of age-appropriate means [13, 14, 15].

b. Food and Drug Administration guidance recommends Cockcroft-Gault formula in adolescents ≥12 years of age and the modified Schwartz formula for infants and children <12 years of age [11].

c. Cockcroft-Gault formula (subjects ≥12 years of age):

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

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

d. Modified Schwartz formula (subjects <12 years of age):

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

K (proportionality constant):

Infant (term <1 year): K=0.45

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

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

## 12.4 List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ASaT	all subjects as treated
AST	aspartate aminotransferase
AUC <sub>0-∞</sub>	area under the concentration time curve
β-hCG	β-human chorionic gonadotropin
BLI	β-lactamase inhibitor
C <sub>EOI</sub>	concentration at end of infusion
CI	coordinating investigator
cIAI	complicated intra-abdominal infection
CL	systemic clearance
C <sub>max</sub>	maximum observed plasma concentration
CMS	colistimethate sodium
CSR	clinical study report
cUTI	complicated urinary tract infection
%CV	coefficient of variation
ECI	event of clinical interest
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
ERC	Ethical Review Committee
FDAAA	Food and Drug Administration Amendments Act
GCP	Good Clinical Practice
HABP	hospital-acquired bacterial pneumonia
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMI	imipenem/cilastatin
IMI/REL	fixed-dose combination of imipenem/cilastatin/relebactam (MK-7655A)
IMP	Imipenemase metallo-β-lactamase
IRB	Institutional Review Board
IV	intravenous (parental)
IVRS	interactive voice response system
IWRS	interactive web response system
KPC	<i>Klebsiella pneumoniae</i> carbapenemase
LAR	legally acceptable representative
M&S	modeling and simulation
MDR	multi-drug resistant
NCA	noncompartmental analysis
NDM-1	New Delhi metallo-β-lactamase 1
OAT	organic anion transporter
OXA	oxacillinase
PIN	personal identification number
PK	pharmacokinetic

<b>Abbreviation</b>	<b>Definition</b>
QTc	corrected measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
REL	relebactam
SAE	serious adverse event
t <sub>1/2</sub>	terminal half-life
TMIC	time spent above the minimum inhibitory concentration
ULN	upper limit of normal
US	United States
VABP	ventilator-associated bacterial pneumonia
V <sub>c</sub>	central volume of distribution
VIM	Verona integron-encoded metallo-β-lactamase
V <sub>ss</sub>	volume of distribution

### 13.0 SIGNATURES

#### 13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

#### 13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	