Official Protocol Title:	A Multicenter, Open-label, Noncomparative, Japanese Phase III Study to Assess the Efficacy and Safety of Ceftolozane/Tazobactam (MK-7625A) in Japanese Patients with Uncomplicated Pyelonephritis and Complicated Urinary Tract Infection
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TITLE:

A Multicenter, Open-label, Noncomparative, Japanese Phase III Study to Assess the Efficacy and Safety of Ceftolozane/Tazobactam (MK-7625A) in Japanese Patients with Uncomplicated Pyelonephritis and Complicated Urinary Tract Infection

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1.0 TRIAL SUMMARY

Abbreviated Title	A Japanese Phase III, Open-label, Noncomparative Trial of MK-7625A in Japanese patients with uncomplicated pyelonephritis and complicated urinary tract infection
Sponsor Product Identifiers	MK-7625A
Trial Phase	Phase III
Clinical Indication	Uncomplicated pyelonephritis and complicated urinary tract infection
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	MK-7625A
Number of trial subjects	Approximately 115 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 13 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial for approximately 6 weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase, each subject will receive MK-7625A for 7 days. After the end of treatment, each subject will be followed for 4 to 5 weeks.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a nonrandomized, multi-site, open-label trial of MK-7625A in Japanese subjects with uncomplicated pyelonephritis and complicated urinary tract infection (cUTI) to be conducted in conformance with Good Clinical Practices.

Approximately 115 subjects with a diagnosis of cUTI including pyelonephritis (uncomplicated or complicated pyelonephritis, and complicated lower UTI) will be enrolled in this trial. The enrollment of the patients with CrCl 30-50 mL/min at screening will be restrained from exceeding 15% (18 patients) of the total enrollment due to the rationale described in 4.2.1. For patients with a diagnosis of pyelonephritis at screening, the enrollment will be restrained from exceeding 80% (92 patients) of the total enrollment. All subjects will receive MK-7625A 1.5 g (ceftolozane 1 g/tazobactam 0.5 g) intravenously (IV) every 8 hours under unblinded conditions. An adjusted dose [MK-7625A 750 mg (ceftolozane 500 mg/tazobactam 250 mg)] will be administered to subjects with creatinine clearance (CrCl) 30-50 mL/min. Each subject will be receiving MK-7625A for 7 days. Efficacy assessments (microbiological response and clinical response) will be conducted at the End of Therapy visit (EOT; within 1 day after the completion of study drug administration) and the Test of Cure visit (TOC; 7 days ±2 days after completion of study drug administration). Subjects will be followed for Efficacy and Safety evaluations until Late Follow-up (LFU; 28 to 35 days after completion of study drug administration).

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 .

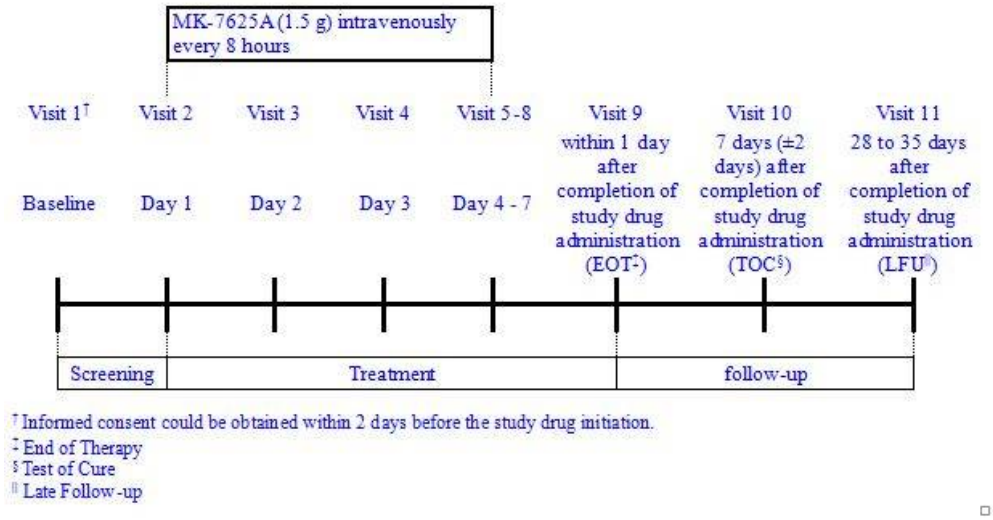


Figure 1 Trial Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

1) **Objective:** To estimate the per-subject microbiological response of MK-7625A in subjects with uncomplicated pyelonephritis and cUTI in the Microbiologically Evaluable (ME) population at TOC.
2) **Objective:** To evaluate the safety and tolerability of MK-7625A in subjects with uncomplicated pyelonephritis and cUTI.

3.2 Secondary Objective(s) & Hypothesis(es)

1) **Objective**: To estimate the per-subject microbiological response of MK-7625A in subjects with uncomplicated pyelonephritis and cUTI in the ME population at EOT and LFU.
2) **Objective**: To estimate the per-subject and per-pathogen microbiological response of MK-7625A in subjects with uncomplicated pyelonephritis and cUTI in the microbiological Modified Intent-to-treat (mMITT) population at EOT, TOC, and LFU, and to estimate the per-pathogen microbiological response of MK-7625A in subjects with uncomplicated pyelonephritis and cUTI in the ME population at EOT, TOC and LFU".

3) **Objective**: To estimate the clinical response of MK-7625A in subjects with uncomplicated pyelonephritis and cUTI in the mMITT and Clinically Evaluable (CE) populations at EOT, TOC, and LFU.

4) **Objective**: To estimate the composite response (based on microbiological response and clinical response) of MK-7625A in subjects with uncomplicated pyelonephritis and cUTI in the ME and mMITT populations at TOC.

3.3 Exploratory Objectives

1) **Objective:** To summarize the proportion of subjects with superinfections or new infections in the mMITT and ME population.

2) **Objective:** To summarize the proportion of subjects with relapse of clinical cure in the mMITT and CE population and recurrence of per-subject and per-pathogen microbiological eradication in the mMITT and ME population.

3) **Objective:** To provide the plasma concentrations of ceftolozane and tazobactam for updating population pharmacokinetic (POP-PK) model.

4) **Objective:** To explore the relationship between genetic variation and response to the treatment(s) administered. Variation across the human genome will be analyzed for association with clinical data collected in this study.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB) for detailed background information on MK-7625A.

4.1.1 Pharmaceutical and Therapeutic Background

Summary of MK-7625A

MK-7625A is a fixed-dose combination of a novel antipseudomonal cephalosporin and a well-established β-lactamase inhibitor (BLI) that has potent in vitro activity against most extended spectrum β-lactamase (ESBL)–producing Enterobacteriaceae and drug-resistant *Pseudomonas aeruginosa*.

Ceftolozane shares the basic chemical and biological attributes and mechanism of action with other β-lactam antibiotics [1] [2]. The primary mechanism of action is inhibition of the transpeptidation step of bacterial peptidoglycan biosynthesis by inactivation of penicillin binding proteins (PBPs). Ceftolozane is a member of the cephalosporin class of antibiotics, which are well characterized in terms of their safety, efficacy, and general antimicrobial profile. Cephalosporin antibiotics have been widely used in clinical practice for many years for their broad antibacterial spectrum, bactericidal activity, and excellent safety profile. A number of third and fourth generation parenteral cephalosporin antibiotics continue to be widely used (e.g., ceftriaxone, cefepime, and ceftazidime), although expanding resistance erodes their reliability. Ceftolozane exhibits time-dependent killing activity against various Gram-negative organisms, including drug-resistant *P. aeruginosa*. Ceftolozane has been shown to be potent against strains of *P. aeruginosa* that are resistant to carbapenems, cephalosporins, fluoroquinolones, and/or aminoglycosides, including the majority of multiple drug-resistant (MDR) isolates. Like most cephalosporins, ceftolozane is poorly active against enterococci, ESBL-producing Enterobacteriaceae, and Gram-negative anaerobes.

Tazobactam is a potent inhibitor of chromosomal- and plasmid-mediated bacterial class A and some class C β-lactamases that, by binding to the active site of these enzymes, protects ceftolozane from hydrolysis, broadening its spectrum to include most ESBL-producing *Escherichia coli*, *Klebsiella pneumoniae*, and other Enterobacteriaceae, as well as some important anaerobic pathogens (i.e., *Bacteroides fragilis*).

MK-7625A does not adequately cover certain pathogens, such as Gram-positive pathogens (*Enterococci*, *Staphylococcus aureus)*, and anaerobes other than *Bacteroides fragilis.*

Epidemiology and Clinical Manifestations of cUTI

The prevalence of urinary tract infections (UTI) is increasing and its financial burden is significant. According to a major epidemiological study conducted in the US, UTI accounts for more than 100,000 hospital admissions annually and up to 40% of all hospital-acquired infections. In addition, the elderly population is now increasing globally. A higher incidence of bacteriuria and UTI is observed in elderly patients, both in long-term care facilities and at home. The management of elderly patients with UTI is increasing in clinical significance. Almost all of UTI in the elderly is cUTI. cUTI is a frequent cause of hospitalization and a common health-care associated complication [3] [4].

cUTI is defined as a clinical syndrome in men or women characterized by the development of systemic and local signs and symptoms of fever, chills, malaise, flank pain, back pain, and costovertebral angle pain or tenderness, occurring in the presence of an abnormality of the urinary tract or in the presence of catheterization. cUTI results from a wide variety of abnormalities including anatomical, structural, or functional alterations of the urinary tract (e.g., urolithiasis, indwelling urethral catheter, intermittent catheterization, stents, prostatic hypertrophy), impaired renal function (e.g., acute renal failure from intra, or post-renal nephropathies or heart failure), and immunocompromised status (e.g., diabetes mellitus, cancer, renal transplant). Clinical presentation can vary, ranging from mild lower urinary tract symptoms such as frequency and/or urgency to systemic symptoms associated with bacteremia and sepsis.

Pyelonephritis, a subset of UTI, is an infection of one or both kidneys that can occur in patients with or without functional or anatomic abnormalities of the urinary tract. Pyelonephritis often presents with both local and systemic signs of infection including flank pain and/or tenderness, fever, and malaise. Both complicated (associated with functional alterations of the urinary tract, impaired renal function or immunocompromised status) and uncomplicated pyelonephritis requires antimicrobial treatment for a similar length of time as other cUTI.

In cUTI, *E.coli* remains the predominant organism, but other aerobic Gram-negative rods, such as *Klebsiella* species, *Proteus* species, *Citrobacter* species, *Acinetobacter* species, *Morganella* species, and *P. aeruginosa*, also are frequently isolated. Gram-positive bacteria (e.g. *Enterococci* and *Staphylococcus aureus*), and yeasts are also important pathogens in cUTI [5].

According to a Japanese nationwide epidemiological survey [6], a total of 688 bacterial strains were isolated from patients diagnosed with cUTI. Among them, 216 patients were hospitalized (31.4%) with preexisting diseases at the time of the study. The following bacterial species were isolated from the hospitalized patients: *Enterococcus faecalis*, 36.4% (51/140), *E. coli*, 22.0% (56/255), *K. pneumoniae*, 34.4% (32/93), *Proteus mirabilis*, 23.8% (10/42), *Serratia marcescens*, 29.5% (13/44), and *P. aeruginosa*, 47.4% (54/114). The proportions of fluoroquinolone-resistant *E. faecalis*, *E.coli*, *P. mirabilis*, and *S. marcescens* strains were 35.7%, 29.3%, 18.3%, and 15.2%, respectively. The proportions of *E. coli*, *P. mirabilis*, *K. pneumoniae*, and *S. marcescens* strains producing ESBL were 5.1%, 11.9%, 0%, and 0%, respectively. The proportions of *P. aeruginosa* strains resistant to carbapenems, aminoglycosides, and fluoroquinolones were 9.2%, 4.4%, and 34.8%, respectively; among them, 2 strains (1.8%) were multidrug resistant.

Treatment of cUTI

Empiric antimicrobial therapy for cUTI should be sufficiently broad spectrum to cover the most commonly isolated pathogens. Treatment should be individualized for the subject, based on subject tolerance, clinical presentation, prior antimicrobial use and urine culture reports, and known or suspected institutional susceptibilities.

The fluoroquinolones and cephalosporins classes have long been widely used for empiric treatment of cUTI. According to Japan Nosocomial Infections Surveillance (JANIS), in five years from 2009 (the number of medical institutions: 499) to 2013 (the number of medical institutions: 745), the percentage of medical institutions that fluoroquinolone- or third generation cephalosporin-resistant *E. coli* was isolated from increased approximately 10%. The percentage of medical institutions that fluoroquinolone-resistant *E. coli* was isolated from rose from 84.6% to 94.9%. The percentage of medical institutions that third generation cephalosporin-resistant *E. coli* was isolated from rose from 81.2% to 89.9%. In 2013, the rate of resistance of *E. coli* against levofloxacin was 35.5% (number of specimen: 155998), the rate of resistance of *E. coli* against cefepime was 10.9% (number of specimen: 81456). Increasing resistance to fluoroquinolone and cephalosporin antimicrobial drugs poses a major medical problem [7].

Although a number of antimicrobial agents are approved for use in cUTI, the emergence of resistance to these agents has created a large unmet medical need.

4.1.2 Clinical Trial results

The prior global cUTI Phase 2 and 3 studies were conducted outside of Japan; hence, there is a need for an additional trial in Japan for this indication.

Phase 1 Trial in Japanese Subjects (CXA-EB-13-05)

An open-label Phase 1 single ascending dose trial (CXA-EB-13-05) was conducted to evaluate pharmacokinetics (PK), safety and tolerability of MK-7625A after a single 1 hr IV infusion of MK-7625A at 1.5 g and 3 g doses. A total of 29 healthy subjects were enrolled (Japanese: 10 subjects, Chinese: 9 subjects and Caucasian: 10 subjects).

The PK of ceftolozane and tazobactam were comparable between the 3 ethnic groups. After dose normalization, the PK parameters were comparable between the 1.5 and 3 g doses for each ethnic group. These findings suggest that the PK is dose independent and similar across the three ethnic groups.

A total of 4 subjects experienced adverse events (AEs) with the single-dose administration of MK-7625A 1.5 g and 1 AE (drug eruption) lead to discontinuation in a Chinese subject [Chinese: 3 subjects (constipation: 2 subjects; faeces discoloured: 1 subject; headache: 1 subject: and drug eruption: 1 subject), Japanese: 1 subject (pharyngitis)].

A total of 3 subjects experienced AEs with the single-dose administration of MK-7625A 3 g [Caucasian: 1 subject (dry mouth and dizziness), Chinese: 2 subjects (abdominal pain: 1 subject; decreased appetite: 1 subject, and yellow skin: 1 subject)]. All AEs in both dosing groups were mild in severity.

Phase 2 Trial in Subjects with cUTI including pyelonephritis (CXA-101-03)

Phase 2 trial (CXA-101-03) evaluated the comparative efficacy and safety of IV ceftolozane (1 g every 8 hours) versus IV ceftazidime (1 g every 8 hours) for 7 to 10 days in hospitalized adult subjects with cUTI including pyelonephritis.

The microbiological response of ceftolozane at TOC (test-of-cure) was comparable to ceftazidime in complicated lower UTI and pyelonephritis. Moreover, ceftolozane was well-tolerated and the incidence of AEs and drug related AEs of ceftolozane was comparable to ceftazidime.

Phase 3 Trials in Subjects with cUTI including pyelonephritis (CXA-cUTI-10-04 and CXA-cUTI-10-05)

In two Phase 3 trials (CXA-cUTI-10-04 and CXA-cUTI-10-05) for cUTI including pyelonephritis, the efficacy and safety of MK-7625A (1.5 g every 8 hours) was compared with levofloxacin (0.75 g once daily). The treatment period was 7 days.

MK-7625A achieved high composite microbiological and clinical cure rates at the TOC visit in the primary (mMITT) and secondary (ME) efficacy populations. For both populations, the lower bound of the 95% CI (2.31, 14.57) around the treatment difference (MK-7625A minus levofloxacin) was greater than -10%, indicating noninferiority. Notably, the 2-sided 99% CI around the treatment differences excluded zero in both primary and key secondary analysis populations indicating superiority over levofloxacin.

The microbiological response rate of MK-7625A at TOC in ME population was 86.2% and 95% CI was (82.2, 89.5). The difference of microbiological response (MK-7625A minus levofloxacin) was 8.6% and 95% CI was (2.87, 14.26).

MK-7625A was well-tolerated. The type, incidence and degree of AEs were comparable between MK-7625A and levofloxacin in the integrated Phase 3 analysis.

4.1.3 Ongoing Clinical Trials

The Phase 3 global trial (Protocol 008) for ventilated nosocomial pneumonia, the Phase 1 PK trial (Protocol 007) for intensive care unit subjects, and the Phase 1 pediatric PK trial (Protocol 010) are on-going. Additional details may be found in the accompanying Investigators Brochure (IB).

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

This open-label trial is planned to estimate the efficacy and safety of MK-7625A for uncomplicated pyelonephritis and cUTI in Japanese patients. The prior global cUTI Phase 2 and 3 studies were conducted outside of Japan; hence, there is a need for an additional trial in Japan for this indication.

Rationale for trial design

The primary data that support the efficacy of MK-7625A in the cUTI indications were derived from 2 large, identical, global, multicenter, randomized, double-blind, active-controlled Phase 3 trials (CXA-cUTI-10-04 and CXA-cUTI-10-05) subsequently pooled to form one submission dataset.

In the cUTI indication, subjects were randomized 1:1 to receive either MK-7625A (1.5 g [1 g of ceftolozane and 0.5 g tazobactam] every 8 hours) or levofloxacin (0.75 g once daily) administered as IV infusions for 7 days. The results indicated MK-7625A was noninferior to levofloxacin for the primary and key secondary efficacy variables. Additionally, the lower bound of the 2-sided 99% CI excluded zero in both the primary and secondary analysis populations, indicating superiority over levofloxacin.

The purpose of this trial is to further demonstrate the safety and efficacy of MK-7625A in only Japanese patients with cUTI for Japanese registration. Therefore, the design of this trial is open-label, non-comparative design for the purpose of collecting safety and efficacy data without statistical verification and assess use of MK-7625A in Japanese patients with cUTI.

Rationale for sample size

A sample size of 74 evaluable patients in the microbiological evaluable (ME) population is applied to the Japanese cUTI trial to achieve a similar microbiological response to that in two global cUTI Phase 3 trials.

The estimated microbiological response rate at TOC for the Japanese subjects is 85.1% with a 95% confidential interval (75.0%, 92.3%) in the ME population. The estimated upper and lower limits of the interval are comparable with the microbiological response rate (86.2%) observed in the global cUTI Phase 3 trials (CXA-cUTI-10-04 and CXA-cUTI-10-05).

The estimation is based on the assumption that microbiological efficacy of MK-7625A is similar between Japanese and non-Japanese subjects. The assumption is supported by the similarity in the MIC distributions for MK-7625A between the clinical isolates collected in Japan and the US & EU, the comparability in PK exposures, and the expected PK-PD relationships between Japanese and non-Japanese subjects. Assuming there will have a 35% dropout rate (from enrollment to who qualifies for the ME population), a total of 115 subjects will be enrolled.

Rationale for Selected Subject Population

The activity of ceftolozane alone and MK-7625A has been well characterized in a comprehensive series of in vivo and in vitro microbiology studies. MK-7625A displays potent time-dependent antibacterial activity against select Gram-positive pathogens, especially *streptococci*, and common Gram-negative aerobic pathogens commonly involved in cUTI, such as *E. coli*, other Enterobacteriaceae, and *P. aeruginosa*. The BLI activity of tazobactam protects ceftolozane from the majority of common ESBL-producing Enterobacteriaceae, an increasing problem in patients with cUTI that is associated with poorer microbiological outcomes compared with patients with ESBL-negative isolates. In addition, MK-7625A is active against strains of *P. aeruginosa* that are resistant to carbapenems, cephalosporins, fluoroquinolones, and aminoglycosides, including isolates exhibiting multidrug resistance.

The primary data that support the safety and efficacy of MK-7625A in cUTI including pyelonephritis indications were derived from 2 large, identical, multicenter, randomized, double-blind, active-controlled Phase 3 trials (CXA-cUTI-10-04 and CXA-cUTI-10-05), subsequently pooled to form 1 submission dataset. The efficacy (composite response based on microbiological response and clinical response) of MK-7625A was non-inferior to levofloxacin which is a comparator drug.

From the above, MK-7625A shows antimicrobial activity against main offending bacterium of cUTI, and the efficacy of MK-7625A in subjects with cUTI including pyelonephritis was shown in overseas trials.

To keep the comparability of safety and efficacy assessment of MK-7625A in Japanese patients to the non-Japanese patients in the global trials, the proportion of patients with moderate renal insufficiency (CrCl 30-50 mL/min) will be capped at 15%. In a subgroup analysis of the Phase 3 cUTI trials (CXA-cUTI-10-04 and CXA-cUTI-10-05), clinical cure rates were lower in patients with baseline creatinine clearance (CrCl) of 30 to ≤50 mL/min (61.8%, 21/34 subjects) compared to those with CrCl >50 mL/min (78.5%, 285/363 subjects). Patients with moderate renal insufficiency are expected to be at worse baseline health and require dose adjustment of MK-7625A. Therefore, the enrollment of the patients with CrCl 30-50 mL/min is limited to 15% (18 patients) of the total enrollment in this study to keep the similar proportion of these patients as the global studies. Similarly, for patients with a diagnosis of pyelonephritis at screening, the enrollment will be restrained from exceeding 80% (92 subjects) of the total enrollment to be comparable to the global trial data [pyelonephritis: 82.4% (328/398 subjects)].

Rationale for the Trial

MIC distributions for MK-7625A against Enterobacteriaceae and *P. aeruginosa*, which represent the target pathogens of MK-7625A, were compared between the clinical isolates collected in Japan (cryopreservation stock strain of the epidemiological purpose) and North America/EU (Clinical Isolates from US, EU, British and Canadian Surveillance Programs showed in IB). The result shows similar MIC distribution among the tested clinical isolates both in Japan and in North America/EU [*E. coli*: MIC_{50} and MIC_{90} are 0.12 µg/mL and 0.5µg/mL in the clinical isolates in Japan (N=100), 0.25 µg/mL and 0.5µg/mL in the clinical isolates in North America/EU (N=9429) respectively. *P. aeruginosa*: MIC_{50} and MIC_{90} are 0.5 µg/mL and 2 µg/mL in the clinical isolates in Japan (N=100), 0.5 µg/mL and 4µg/mL in the clinical isolates in North America/EU (N=6316) respectively].

A single-dose, open-label, parallel-group trial (CXA-EB-13-05) to evaluate the pharmacokinetics, safety and tolerability of MK-7625A after single intravenous infusion to adult Japanese, Chinese and Caucasian healthy subjects, was conducted. After dose and/or weight normalization, AUC and C_{max} values were similar between ethnic groups. Thus, it can be concluded that no clinically relevant difference in PK behavior is observed for ceftolozane, tazobactam and tazobactam M1 in all the healthy subjects investigated.

From the above, it was thought possible to use overseas study results as reference data. In Japan, the Japanese Phase 3 trial (Protocol 014) is planned to examine and confirm the efficacy (microbiological response and clinical effect) and safety of the overseas Phase 3 studies for cUTI including pyelonephritis.

4.2.2 Rationale for Dose Selection/Regimen/Modification

In this Japanese Phase 3 trial (Protocol 014), subjects with CrCl > 50 mL/min will receive MK-7625A 1.5 g (ceftolozane 1 g/tazobactam 0.5 g) and subjects with CrCl 30 - 50 mL/min will receive MK-7625A 750 mg (ceftolozane 500 mg/tazobactam 250 mg).

The dose selection of the ceftolozane component of MK-7625A was mainly based on the PK of ceftolozane and all known relevant pharmacokinetic/pharmacodynamic (PK/PD) principles for cephalosporins. The dose of tazobactam was based on prior experience with BLIs and aimed to achieve a dose known to be well-tolerated. Based on the combined plasma concentration-time data from Phase 1 and 2 trials, a population PK analysis was conducted to characterize the PK of ceftolozane, and using these data, Monte Carlo simulations were conducted to evaluate the expected efficacy of different dosing regimens of ceftolozane. Like other β-lactam antibiotics, the PK/PD parameter that most closely correlates with efficacy is the time, as a percentage of the dosing interval, that the plasma concentration of ceftolozane exceeds the minimum inhibitory concentration (MIC) of the infecting organism (%T>MIC). Monte Carlo simulation analysis of clinical PK data revealed that using 30% T>MIC, an IV 1-hour infusion of 1.5 g MK-7625A administered every 8 hours would provide sufficient drug concentrations to cover target pathogens, with a probability of target attainment (PTA) of 100% for pathogens with an MIC of up to 8 µg/mL.

MK-7625A 1.5 g every 8 hours intravenously demonstrated non-inferiority of efficacy to levofloxacin 0.75 g once daily intravenously in Phase 3 trials (CXA-cUTI-10-04 and CXA-cUTI-10-05) for cUTI including pyelonephritis. Additionally, MK-7625A 1.5 g every 8 hours intravenously demonstrated non-inferiority of efficacy to meropenem 1 g every 8 hours intravenously in Phase 3 trials (CXA-cIAI-10-08 and CXA-cIAI-10-09) for complicated intra-abdominal infectious. MK-7625A 1.5 g every 8 hours intravenously was generally well-tolerated.

The PK of MK-7625A has also been evaluated in subjects with mild, moderate, and severe renal impairment, as well as subjects with end-stage renal disease on hemodialysis (CXA-101-02, CXA-201-02, and CXA-REN-11-01). Each trial evaluated a single-dose based on the linear and time independent PK profile of MK-7625A.

Relative to MK-7625A exposures in subjects with normal renal function (CrCl ≥90 mL/min), no clinically relevant differences in exposure were observed in subjects with mild renal impairment, whereas exposures increased approximately 2-fold in subjects with moderate renal impairment.

Based on these results, no dose adjustment is recommended for subjects with mild renal impairment (CrCl >50 to 89 mL/min). However the MK-7625A dose in subjects with moderate renal impairment (CrCl >30 to 50 mL/min) is recommended to be reduced by 2-fold (i.e., 750 mg MK-7625A every 8 hours).

The results of the PK/PD target attainment analyses for MK-7625A 1.5 g (ceftolozane 1 g/tazobactam 0.5 g) and dosing regimens adjusted for renal function described below, which are based on non-clinical PK/PD targets for ceftolozane alone and as appropriate, in combination with those for tazobactam, against Enterobacteriaceae from the clinical trial program, support in vitro susceptibility test interpretive criteria for MK-7625A against Enterobacteriaceae of 2-4 μg/mL:

- For patients with normal renal function administered MK-7625A 1.5 g (ceftolozane 1 g/tazobactam 0.5 g) q8h, a PK/PD MIC cutoff value of as high as 4 μg/mL was identified;

- For patients with mild renal impairment administered MK-7625A 1.5 g (ceftolozane 1 g/tazobactam 0.5 g) q8h, a PK/PD MIC cutoff value of as high as 8 μg/mL was identified; and

- For patients with moderate renal impairment administered MK-7625A 750 mg (ceftolozane 500 mg/tazobactam 250 mg) q8h, a PK/PD MIC cutoff value of as high as 8 μg/mL was identified.

The treatment period of MK-7625A for this Japanese Phase 3 trial (Protocol 014) is 7 days, based on 2 overseas Phase 3 studies (CXA-cUTI-10-04 and CXA-cUTI-10-05) for cUTI including pyelonephritis and the US package insert.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

In this Japanese Phase 3 trial (Protocol 014), microbiological response (primary endpoint) and clinical response are set as efficacy endpoints. Clinical response and microbiological response are the efficacy endpoints that will be used to estimate the efficacy of MK-7625A based on the clinical signs and symptoms (Section 7.1.2.3), microbiological outcome (Section 7.1.3.3), and clinical outcome (Section 7.1.2.4).

In order to estimate the efficacy of MK-7625A to the uropathogen isolated from subjects with uncomplicated pyelonephritis and cUTI which are target diseases of this clinical trial, the evaluation criteria of the microbiological response is set as the index of bacterial colony forming unit by urine culture. Moreover, in this clinical trial, in order to observe change of clinical signs and symptoms for uncomplicated pyelonephritis and cUTI, the evaluation criteria of clinical response are set.

In addition, there is also the condition of asymptomatic bacteriuria without clinical signs/symptom of infection in cUTI. Therefore, microbiological response is set as primary endpoint for efficacy.

Based on the Japanese guideline (the 1st edition) for urinary tract/genital infection, TOC is set as primary time point for efficacy. Moreover, in order to estimate the efficacy at the end of treatment of MK-7625A, EOT is set as secondary time point for efficacy. The analysis populations in the study objectives are comparable to those of global cUTI studies (CXA-cUTI-10-04 and CXA- cUTI-10-05). The same mMITT, CE and ME population definitions included in both the global trial and this trial are used for the analysis of clinical response/microbiological response.

4.2.3.1.1 Definition of Efficacy Endpoints

Refer to Table 1 for efficacy endpoints by timing and analysis population. Details of the endpoints are presented in the referenced sections.

Table 1 Summary of Efficacy Endpoints

Objective	Endpoint	Timing	Analysis Population	References (Section)
Primary	Per-subject Microbiological response	TOC	ME	7.1.3.3
Secondary	Per-subject microbiological response	EOT, LFU	ME	7.1.3.3
		EOT, TOC and LFU	mMITT	
	Per-pathogen microbiological response	EOT, TOC and LFU	ME	
		EOT, TOC and LFU	mMITT	
	Clinical Response	EOT, TOC and LFU	CE	7.1.2.4
		EOT, TOC, and LFU	mMITT	
	Composite (microbiological and clinical) response	TOC	ME	7.1.3.5
			mMITT	

4.2.3.2 Safety Endpoints

In this Japanese Phase 3 trial (Protocol 014), vital signs, AEs (clinical AEs and laboratory AEs) and laboratory test (hematology test, coagulation test, blood biochemistry test and urine test) are set as safety endpoints in order to evaluate the safety and tolerability of MK-7625A.

The broad clinical and laboratory AE categories consisting of the percentage of patients with any AE, a drug-related AE, a serious AE, and an AE which is both drug-related and serious, and who discontinued the study drug due to an AE will be considered key safety endpoints.

4.2.3.3 Pharmacokinetic Endpoints

Plasma samples for pharmacokinetic analyses will be drawn from all patients that receive MK-7625A. The Plasma concentrations of ceftolozane, tazobactam and its metabolite, tazobactam M1 will be summarized and the plasma concentration data of ceftolozane and tazobactam will be used for POP-PK analysis. All available data for the POP-PK analysis will be used for the analysis. The parameters to be evaluated for the POP-PK analysis will be specified in a separate POP-PK protocol.

4.2.3.4 Pharmacodynamic Endpoints

The pharmacokinetic/pharmacodynamic analyses will be specified in a separate protocol.

4.2.3.5 Planned Exploratory Biomarker Research

Planned Genetic Analysis

Understanding genetic determinants of drug response is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population. This research contributes to understanding genetic determinants of efficacy and safety associated with the treatments in this study.

4.2.3.6 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on DNA specimens collected for future biomedical research during this clinical trial.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Japanese Male/Female subjects with uncomplicated pyelonephritis or cUTI of at least 18 years 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. Provided written informed consent prior to any study-related procedure not part of normal medical care (a legally acceptable representative may provide consent if the subject is unable to do so, provided this is approved by local country and institution specific guidelines). The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research. The written informed consent should also be obtained from a legally acceptable representative if the subject is < 20 years of age.
2. Be Japanese males or females ≥ 18 years of age who needs hospitalization.
3. Pyuria (white blood cell [WBC] count > 10/μL in unspun urine or ≥ 10 per high power field in spun urine) at screening visit.
4. Clinical signs and/or symptoms of UTI at screening visit, either of 1) or 2):
    1) Pyelonephritis (uncomplicated or complicated), as indicated by at least 2 of the following:
        a. Documented fever (oral temperature > 38°C or axillary temperature >37.5°C) accompanied by patient symptoms of rigors, chills, or warmth
        b. Flank pain
        c. Costovertebral angle tenderness or suprapubic tenderness on physical exam
        d. Nausea or vomiting

2) Complicated lower UTI, as indicated by the following 2 symptoms and 1 complicating factor:

   a. At least 2 of the following new or worsening symptoms of complicated lower UTI:

      i. Dysuria; urinary frequency or urinary urgency

      ii. Documented fever (oral temperature > 38.0°C or axillary temperature >37.5°C) accompanied by patient symptoms of rigors, chills, or warmth

      iii. Suprapubic pain or flank pain

      iv. Costovertebral angle tenderness or suprapubic tenderness on physical exam

      v. Nausea or vomiting

   b. And at least 1 of the following complicating factors:

      i. Males with documented history of urinary retention

      ii. Indwelling urinary catheter that is scheduled to be removed during IV study therapy and before the EOT

      iii. Current obstructive uropathy that is scheduled to be medically or surgically relieved during IV study therapy and before the EOT

      iv. Any functional or anatomical abnormality of the urogenital tract (including anatomic malformations or neurogenic bladder) with voiding disturbance resulting in at least 100 mL residual urine.

5. Have a pretreatment baseline urine culture specimen obtained within 24 hours before the start of administration of the first dose of study drug.

   NOTE: Subjects may be enrolled in this study and start IV study drug therapy before the Investigator knows the results of the baseline urine culture.

6. Require IV antibacterial therapy for the treatment of the presumed UTI.

7. If female, subject is either:

   1) Not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile due to bilateral tubal ligation, bilateral oophorectomy, or hysterectomy, no possibility of pregnancy based on pregnancy tests (urine hCG, etc.) or lactating.

2) Of childbearing potential and is practicing a barrier method of birth control [e.g., a diaphragm or contraceptive sponge (unapproved in Japan)] along with 1 of the following methods: oral or parenteral (unapproved in Japan) contraceptives (for 3 months prior to study drug administration), or a vasectomized partner. Or, the subject is practicing abstinence from sexual intercourse. Subjects must be willing to practice these methods for the duration of the trial and for at least 35 days after last dose of study medication.

8. Males are required to practice reliable birth control methods (practicing abstinence from sexual intercourse, condom or other barrier device) during the conduct of the study and for at least 75 days after last dose of study medication.

5.1.3 Subject Exclusion Criteria

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

1. Subject with history of recent or recurrent Gram-positive organism UTI suggesting colonization, or subject with UTI that shows or suspects the presence of a Gram-positive organism only.
2. Have a documented history of any moderate or severe hypersensitivity or allergic reaction to any β-lactam antibacterial including cephalosporins, carbapenems and penicillins, or tazobactam.
3. Have a concomitant infection at the time of randomization, which requires non-study systemic antibacterial therapy in addition to IV study drug therapy [vancomycin, linezolid, daptomycin and teicoplanin (i.e. drugs with only Gram-positive activity) are allowed].
4. Subject who are currently receiving probenecid.
5. Subject who are currently receiving bladder infusions with topical urinary antiseptics or antibacterial agents.
6. Receipt of any dose of a potentially therapeutic systemic antibacterial agent for the treatment of the current UTI within 48 hours before the study-qualifying pretreatment baseline urine is obtained.

   (exceptions: subjects with an active UTI who have received prior systemic antibiotics may be enrolled provided a minimum of 48 hours have elapsed between the last dose of the prior systemic antibiotic and the time of obtaining the baseline urine specimen).
7. Receipt of any amount of potentially therapeutic systemic antibacterial therapy after collection of the pretreatment baseline urine culture and before administration of the first dose of study drug.
8. Intractable urinary infection at baseline that the Investigator anticipates would require more than 7 days of study drug therapy.
9. Complete, permanent obstruction of the urinary tract.
10. Confirmed fungal urinary tract infection at time of randomization (with $\geq 10^3$ fungal CFU/mL).

11. Permanent indwelling bladder catheter or urinary stent including nephrostomy.
12. Suspected or confirmed perinephric or intrarenal abscess.
13. Suspected or confirmed prostatitis, urethritis or epididymitis.
14. Ileal loop or known vesico-ureteral reflux.
15. Severe impairment of renal function including an estimated CrCl < 30 mL/min, requirement for peritoneal dialysis, hemodialysis or hemofiltration, or oliguria (< 20 mL/h urine output over 24 hours) at screening visit. (Refer to Section 5.2.1.1, where the formula for the calculation of CrCl can be found).
16. Current urinary catheter that is not scheduled to be removed before the EOT (intermittent straight catheterization during the IV study drug administration period is acceptable).
17. Any condition or circumstance that, in the opinion of the Investigator, would compromise the safety of the subject or the quality of study data.
18. Subject is judged inappropriate for study by the investigator or sub-investigator.
19. Any rapidly progressing disease or immediately life-threatening illness including acute hepatic failure, respiratory failure, and septic shock.
20. Immunocompromising condition, including established AIDS, hematological malignancy, or bone marrow transplantation, or immunosuppressive therapy including cancer chemotherapy, medications for prevention of organ transplantation rejection, or the administration of corticosteroids equivalent to or greater than 40 mg of prednisone per day administered continuously for more than 14 days preceding randomization.
21. One or more of the following laboratory abnormalities at screening visit:
    1) aspartate aminotransferase (AST [SGOT]), alanine aminotransferase (ALT [SGPT]), alkaline phosphatase, or total bilirubin level greater than 3 times the upper limit of normal (ULN)
    2) ALT (SGPT) or AST (SGOT) $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ ULN and, at the same time, Alkaline phosphatase (ALP) $< 2 \times$ ULN
    3) Absolute neutrophil count less than 500/μL
    4) Platelet count less than 40,000/μL
    5) Hematocrit less than 20%.
22. Participation in any clinical study of an investigational product within 30 days prior to the proposed first day of study drug.
23. Previous participation in any study of ceftolozane or MK-7625A.
24. 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 2.

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
MK-7625A	1.5 g (ceftolozane 1 g/tazobactam 0.5 g) 750 mg[†](ceftolozane 500 mg/tazobactam 250 mg)	Every 8 hours	Intravenous	60 (±10) min intravenous infusion/7 days	Experimental
[†] For subjects with CrCl:30-50 mL/min.					

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)

For the subject to whom the renal function decreased, it is necessary to adjust dosage based on the grade of a renal function (creatinine clearance: CrCl). Estimate the subject's CrCl using the subject's serum creatinine value, actual body weight, and the appropriate Cockroft-Gault formula below. For patients with changing renal function (creatinine clearance is either close to 30 or close to 50 mL/min), monitor CrCl at least daily and adjust the dosage of MK-7625A accordingly (dose reduction or dose increase after dose reduction).

For serum creatinine reported in mg/dL:

$$\text{Males:}\quad \text{CrCl (mL/min)} = \frac{(140 - \text{age in years}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

$$\text{Females: CrCl (mL/min)} = 0.85 \times \frac{(140 - \text{age in years}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

The dosage of MK-7625A for each creatinine clearance category is shown in Table 3.

Table 3 The dosage of MK-7625A for every creatinine clearance

Creatinine clearance	Dosage of MK-7625A
CrCl > 50 mL/min	1.5 g (ceftolozane 1 g/tazobactam 0.5 g) IV q8h
CrCl 30 – 50 mL/min	Decrease dose to 750 mg (ceftolozane 500 mg/tazobactam 250 mg) IV q8h
CrCl < 30 mL/min	Discontinue study drug

5.2.2 Timing of Dose Administration

After all the study procedures at visit 1 (baseline) are completed, MK-7625A 1.5 g (ceftolozane 1 g/tazobactam 0.5 g) is administered intravenously every 8 hours starting on visit 2 (Day 1). The dosage of MK-7625A is adjusted for subjects with creatinine clearance 30 - 50 mL/min. Preparation of MK-7625A is referred to in a separate manual.

In this trial, MK-7625A 1.5 g is administered intravenously over 60 (±10) minutes. The second dose is administrated at interval of 8 hour (±4 hours) following the initial dose of study drug. The 3rd dose or subsequent ones are administrated at interval of 8 hour (±2 hours) following the previous infusion. Allowance of administration interval is permitted to facilitate adjustment of the q8h dosing schedule to be carried out throughout the dosing period.

Study drug should be administered daily for exactly 7 full days. This translates to 21 doses of MK-7625A for every 8 hour (q8h) dosing. In addition, a switch to another oral antimicrobial drug during MK-7625A treatment period is not allowed.

5.2.3 Trial Blinding/Masking

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

5.3 Randomization or Treatment Allocation

Subjects participating in this trial will be allocated by non-random assignment. Assignment of treatment/randomization number (see Section 7.1.1.7) will occur centrally using an interactive voice response system/integrated web response system (IVRS/IWRS). In addition, the enrollment of the patients with CrCl 30-50 mL/min at screening will be restrained from exceeding 15% (18 patients) of the total enrollment. For patients with a diagnosis of pyelonephritis at screening, the enrollment will be restrained from exceeding 80% (92 patients) of the total enrollment.

5.4 Stratification

No stratification based on age, sex or other characteristics will be used in this trial.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

5.5.1 Prohibited medicine

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. 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.

Concomitant use of the following medicines is prohibited.

1) Systemic antimicrobial (except for MK-7625A): from the time that the pretreatment baseline urine culture is obtained to LFU visit. (Exception: subjects with clinical or microbiological failure can receive systemic antimicrobial drugs).
2) Other investigational drugs (except for MK-7625A): from 30 days prior to the proposed first day of study drug to LFU visit.
3) Bladder infusions with topical urinary antiseptics or antibacterial agents: from initial dose of study drug to LFU visit.
4) Probenecid: from initial dose of study drug to EOT visit.

5.5.2 Allowed medicine

Systemic medicines (IV or PO) with only Gram-positive activity (i.e., vancomycin, linezolid, daptomycin and teicoplanin) are allowed as concomitant drug: from the pretreatment baseline urine culture to LFU visit.

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

Special care won't be needed for diet and activity.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.4 – Other Procedures.

In this trial, a subject may discontinue from treatment but continue to participate in the regularly scheduled activities, as long as the subject does not withdraw consent.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.

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

- Lack of a qualifying baseline urine culture, as defined in Section 7.1.3.2 (e.g. bacterial counts in urine are $< 10^5$ CFU/mL or coagulase-negative *staphylococci* is isolated).

- Lack of qualifying baseline uropathogen: The subject with Gram-positive organism only at baseline urine culture
- Development of severe impairment of renal function (estimated CrCl <30 mL/min), oliguria (<20 mL/h urine output over 24 hours) or requirement for hemodialysis/hemofiltration.
- Lack of efficacy: New signs and symptoms that develop after 48 hours of study therapy and require additional or alternative antimicrobial therapy [excluding medicines with only Gram-positive activity (i.e., vancomycin, linezolid, daptomycin and teicoplanin)] for the current UTI.
- The case that subject experiences significant adverse event(s) (clinical signs & symptoms or abnormal clinical laboratory test) that is considered study drug-related by investigators and precludes the continuation of study therapy.
- Others (i.e., the subject become pregnant)

5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues 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

	Screening	Treatment					Follow-up	
Visit	1	2	3	4	5-8	9	10	11
Scheduled Day	Baseline	Day 1	Day 2[1]	Day 3[1]	Day 4~7[1]	End of Therapy (EOT)	7 days after completion of study drug administration (TOC)	28-35 days after completion of study drug administration (LFU)
Allowance Day	-1 to the first dose of study drug	-	-	-	-	+1	±2	-
Administrative Procedures								
Informed Consent[2]	X							
Informed Consent for Future Biomedical Research[2]	X							
Inclusion/Exclusion Criteria	X							
Subject Identification Card	X							
Height and body weight	X							
Medical history	X							
Prior and concomitant medication	X	X	X	X	X	X	X	X
Allocation of treatment assignment		X						
Administration of MK-7625A[3]		X	X	X	X	X		
Monitor compliance with Trial Medication		X	X	X	X	X		
Clinical Procedures/Assessments								
Vital sign (oral or axillary body temperature, blood pressure, pulse rate and respiratory rate)	X	X	X	X	X	X	X	X
Physical examination	X	(X)	(X)	(X)	(X)	X	(X)	(X)
Clinical sign/symptom assessment for UTI	X	X	X	X	X	X	X	X
Assess clinical outcome						X	X	X
Assess for adverse events	X	X	X	X	X	X	X	X
Laboratory Procedures/Assessments								
Urine culture and assess pathogen	X			X[4]	(X)	X	X	X
Blood culture and assess pathogen	X[5]	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Urine test for pyuria	X							

Hematology test, blood biochemistry test and urine test	X[6]			X		X	X	X
Coombs test (direct)	X					X		
Assessment of CrCl and Daily Adjustment of Study Therapy Dose as Needed	X	X	X	X	(X)[7]	(X)[7]		
Collect the blood sample for PK[8]		X		X				
Urine pregnancy test (females for child bearing potential)[9]	X							
Blood for Genetic Analysis[10]		X						

X: must be done. X in the Day 4-7 (Visits 5-8) signifies that the procedure should be performed daily.

(X): may be done in case of clinically necessary by primary or sub investigator, and items should be recorded in the source document and eCRF.

Assessment or test result done in 'Day -1 to pre-treatment' can be used as screening result/baseline data even if those are done before informed consent is obtained.

If the Visit 1 and 2 occur on the same day, the procedures required in both Visit 1 and 2 do not need to be repeated.

1. For study Day 2 through 7 all study assessments are to be performed at a consistent time of day for the study patient for each calendar day.
2. It can be done within 2 days prior to study drug initiation.
3. Study drug should be administered daily for 7 full days. This translates to 21 doses of MK-7625A for every 8 hour (q8h) dosing.
4. In case that bacterial count is $\geq 10^4$ CFU/mL in urine culture at Day 3 [allowance: +2 days (Day 4 or Day 5)], the urine specimens for culture will be collected and urine culture will be performed. The same procedure is repeated at the following visit if bacterial count is $\geq 10^4$ CFU/mL in urine culture during treatment period.
5. Culture for blood sample at screening is conducted as indicated in subjects who present with clinical signs and/or symptoms of pyelonephritis or bacteremia (OR subjects with indwelling catheters whose baseline urine specimen are obtained through the catheter). Two sets (from two separate blood draws) of blood cultures (each set consisting of an aerobic bottle) are conducted. Blood culture is conducted at appropriate frequency until negative if the previous blood culture was positive. In addition, if signs of sepsis appear at any time on study, a blood culture should be taken. When blood cultures are indicated, two sets (each set consisting of an aerobic bottle) should be obtained for a total of two aerobic bottles.
6. Local laboratory data is used for enrollment criteria of laboratory test. The samples for laboratory tests of baseline are collected separately, and a sample is sent to a central laboratory. The sampling on Day 3 has allowance: +2 days (Day 4 or Day 5).
7. During this study period, serum creatinine value to determine dose adjustment will be collected in local laboratory. CrCl assessments are set on Day 1 to 3 for all subjects and dose adjustment should be done as appropriate. In addition, for patients with changing renal function (creatinine clearance is either close to 30 or close to 50 mL/min) during the period of Day 4 to 7, obtain serum creatinine value and monitor CrCl at least daily and adjust the dosage of MK-7625A accordingly based on local laboratory results.
8. Blood sample for pharmacokinetics is collected at Day 1 (prior to first dose of study drug) and Day 3 [allowance: +2 days (Day 4 or Day 5)]. 6 samples in total are collected [Day 1: pre-treatment, Day 3: pre-treatment (15 minutes prior to infusion), just before the completion of infusion, 30-90 minutes after the completion of infusion, 2.5-3.5 hours after the completion of infusion and 5.5-7 hours after the completion of infusion]. At least 3 samples must be collected in total if it is difficult to collect all blood samples at Day 3 [Any one of 30-90 minutes after the completion of infusion, 2.5-3.5 hours after the completion of infusion or 5.5-7 hours after the completion of infusion will be collected in addition to pre-treatment (15 minutes prior to infusion) and just before the completion of infusion]
9. A urine pregnancy test (urine hCG) is performed in each investigational institution in female subjects. After checking the urine hCG negative, a subject may be enrolled in this trial.
10. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

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 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

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

7.1.1.1.1 General Informed Consent

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

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

The initial informed consent form, any subsequent revised written informed consent 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 form or addendum to the original consent 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 form template at the protocol level.

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

All subjects 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.

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

At baseline, medical history will be obtained by the investigator or qualified designee. Obtain recent (within past 5 years) medical history.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

At baseline, the investigator or qualified designee will review prior medication use, and record prior medication taken by the subject within 7 days before first dose of trial medication (for all antibacterial agents within 14 days before the first dose of trial medication, other investigational drugs from 30 days before the first dose of trial medication).

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial (from the first dose of trial medication to LFU).

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.

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 (Medication)

Interruptions from the protocol specified treatment plan for compliance <80% require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of trial medication will be witnessed by the investigator and/or trial staff.

7.1.1.9 Height and Body Weight

The investigator or qualified designee will record height and body weight. Body weight (kg) will be measured without shoes or jacket.

7.1.2 Clinical Procedures/Assessments

In order to minimize variability, it is preferred that the same individual(s) perform the same procedure(s)/evaluation(s) for all subjects at each trial site.

7.1.2.1 Physical Examination

The investigator or qualified designee will perform a physical examination. The screening physical examination will be complete; the EOT visit physical examination may be targeted. At other times, the investigator or qualified designee always can perform a complete or targeted physical examination if they suspect an AE or abnormality. A complete physical examination includes examination of body systems (including, but not limited to, general appearance, skin, neck, eyes, ears, nose, throat, breast, lungs, heart, abdomen, back, lymph nodes, extremities, and nervous system). The targeted physical examination should be focused, at the investigator's discretion, based on the subject's condition and circumstances. The targeted physical examination should note any changes in the subject's condition (body systems) since the last assessment and does not preclude examination of any of the body systems as clinically indicated. Clinically significant changes, in the judgment of the Investigator, in physical examination findings (abnormalities) will be recorded as AEs.

7.1.2.2 Vital Sign

The investigator or qualified designee will record vital sign (body temperature (oral or axillary), blood pressure, pulse rate and respiratory rate). Systolic and diastolic blood pressure will be measured on the same arm. Pulse will be recorded simultaneously with blood pressure measurements.

7.1.2.3 Assessment of Clinical Sign/Symptom for UTI

The clinical sign/symptoms of uncomplicated pyelonephritis and cUTI (dysuria, frequency, urgency, flank pain, suprapubic pain/tenderness, chills or rigors, costovertebral angle tenderness, nausea or vomiting) will be evaluated and graded as none, mild, moderate, or severe at the visits specified in the flowchart (Section 6.0).

The definition of grade

1) None: sign or symptom absent
2) Mild: awareness of sign or symptom, but easily tolerated
3) Moderate: sign or symptom of enough intensity to cause interference with usual activity
4) Severe: sign or symptom of enough intensity to incapacitate

7.1.2.4 Assessment for Clinical Outcome

7.1.2.4.1 Clinical Response at the EOT, TOC and LFU Visits

Clinical outcomes will be assessed at both the EOT, TOC and LFU visits. The definition of clinical response is shown in Table 4.

The Investigator will classify clinical outcome as "clinical cure", "clinical failure", or "indeterminate". A favorable clinical response is "clinical cure".

Relapse of clinical cure is defined as a response of clinical failure at LFU for subjects who have a response of clinical cure at TOC.

Table 4 Clinical Response Definitions at the EOT, TOC and LFU Visits

Outcome	Definition
Clinical Cure	Complete resolution of, marked improvement in (where clinical improvement was defined as a reduction in severity of all baseline signs and symptoms with worsening of none and with no requirement for additional antibiotic therapy after EOT), or return to pre-infection signs and symptoms and no use of additional or nonstudy antimicrobial therapy for the treatment of the current UTI.
Clinical Failure	Persistence of 1 or more sign or symptom of infection or reappearance of or new signs and symptoms that requires additional or alternative antimicrobial therapy for the current UTI OR Adverse event leading to study drug discontinuation and the subject required nonstudy antimicrobial therapy for the current UTI.
Indeterminate	Study data were not available for the evaluation of clinical outcome for any reason or the outcome assessment was confounded.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

7.1.3.1 Urine Test for Pyuria

Urine test for pyuria will be conducted and pyuria (white blood cell [WBC] count >10/µL in unspun urine ≥ 10 per high power field in spun urine) will be checked in each investigational institution.

7.1.3.2 Culture (Urine and Blood)

7.1.3.2.1 Urine Culture

A study-qualifying pretreatment baseline urine culture specimen must be obtained within 1 day before the start of administration of the first dose of study drug and at least 48 hours after the last dose of a potentially therapeutic antibacterial agent administered for treatment of the current UTI. If more than 1 appropriately collected urine culture specimen is obtained before the initiation of study drug therapy, the specimen obtained closest to the time of the administration of the first dose of study drug will be considered the baseline specimen.

Urine must be collected either by an adequate midstream clean catch, by catheterization, or by suprapubic aspiration. Urine specimens obtained from Foley bags are not allowed. A study-qualifying pretreatment baseline urine culture must grow at least 1 and not more than 2 bacterial isolates at $\geq 10^5$ CFU/mL each, as follows:

- For non-catheterized subjects, if more than 2 bacterial isolates are identified from a single urine specimen, the culture will be suspected contaminated. Reconfirm the appropriateness of a urine specimen and make an effort to specify a causative uropathogen. If a pathogen of $\geq 10^5$ CFU/mL at baseline urine culture is isolated also from the blood culture at baseline, that pathogen will be considered as a causative pathogen.
- For catheterized subjects, if more than 1 bacterial isolates are identified from a single urine specimen, the culture will be suspected contaminated. Reconfirm the appropriateness of a urine specimen and make an effort to specify a causative uropathogen. If a pathogen of $\geq 10^5$ CFU/mL at baseline urine culture is isolated also from the blood culture at baseline, that pathogen will be considered as a causative pathogen.
- The following pathogens will not be considered causative pathogens of cUTI in this trial.
    - Coagulase-negative *Staphylococci*
    - non-Group D *Streptococci*

      Note: The Lancefield[8] category is shown below as reference.

        - Group A: *Streptococcus pyogenes*
        - Group B: *S. agalactiae*
        - Group C and G: *S. equi, S. canis*

Urine culture, isolation of uropathogen(s), initial identification of pathogen(s) and bacterial counts in urine will be conducted in local laboratory. The result of culture, initial identification of pathogen(s) and bacterial counts at local laboratory should be recorded in the source document and eCRF. The sites should ship the isolated pathogen(s) to the central laboratory because re-identification of uropathogen(s) and MIC test will be performed by central laboratory. Further details of the procedures to be followed for sample collection, storage, and shipment will be documented in the Laboratory Manual.

7.1.3.2.2 Blood Culture

Culture for blood sample at screening is conducted as indicated in subjects with indwelling catheters whose baseline urine specimen are obtained through the catheter or in subjects who present with clinical signs and/or symptoms of pyelonephritis or bacteremia. In addition, if signs of sepsis appear at any time on study, a blood culture should be taken. Blood culture is conducted at appropriate frequency until negative if the previous blood culture was positive.

Blood specimen will be obtained from 2 separate sites, and will be added to each aerobic bottle (a total of 2 aerobic bottles). Culture of the blood specimen, isolation of pathogen(s) and initial identification of pathogen(s) will be conducted in local laboratory. The result of culture and initial identification of pathogen(s) at local laboratory should be recorded in the source document and eCRF. The sites should ship the isolated pathogen(s) to the central laboratory because re-identification and MIC test of pathogen(s) will be performed by central laboratory. Further details of the procedures to be followed for sample collection, storage, and shipment will be documented in a Laboratory Manual.

7.1.3.3 Assessment for Microbiological Outcome

7.1.3.3.1 Microbiological Response at the EOT, TOC and LFU Visits

Microbiological outcomes will be assessed at both the EOT, TOC and LFU visits. The definition of microbiological response is shown in Table 5.

The per-pathogen microbiological outcome will be determined for each uropathogen isolated at baseline from a pretreatment study-qualifying culture. Microbiological outcome is classified as "Eradication", "Persistence" or "Indeterminate." A favorable microbiological response is "Eradication".

The per-subject microbiological response will be determined based on individual outcomes for each baseline uropathogen. In order for a subject to have an overall outcome of microbiological eradication, the outcome for each baseline uropathogen must be eradication. If the outcome for any uropathogen is persistence, the subject will be considered to have an overall microbiological response of persistence.

Recurrence of per-pathogen microbiological eradication is defined as a response of persistence at LFU for subjects who have a response of eradication at TOC. Recurrence of per-subject microbiological eradication is defined as a response of persistence at LFU for subjects who have a response of eradication at TOC.

Table 5 Microbiological Response Definitions at the EOT, TOC and LFU Visits

Outcome	Definition
Eradication	A urine culture shows all uropathogens found at baseline at $\geq 10^5$ CFU/mL were reduced to $<10^4$ CFU/mL.
Persistence	A urine culture, taken any time after the completion of therapy, grows $\geq 10^4$ CFU/mL of the uropathogen found at baseline.
Indeterminate	No interpretable urine culture available.

7.1.3.4 Emergent Infection

Emergent infections (uropathogens other than the baseline uropathogens) will be evaluated at TOC and LFU visit. Uropathogens other than the baseline uropathogens will be classified as "superinfection" or "new infection". The definition of emergent infection is shown in Table 6.

Table 6 Emergent Infection Definitions at the TOC and LFU Visits

Outcome	Definition
Superinfection	A urine culture that grew $\geq 10^5$ CFU/mL of a bacterial uropathogen other than the baseline uropathogen(s) during the course of study drug therapy
New infection	A urine culture that grew $\geq 10^5$ CFU/mL of a bacterial uropathogen other than the baseline uropathogen(s) at any time between the last administration of the last dose of study drug therapy and the LFU visit.

7.1.3.5 Composite Microbiological and Clinical Response

Composite response (based on microbiological response and clinical response) will be assessed at TOC. The definition of microbiological response is shown in Table 7.

The composite response will be classified as "cure", "failure", or "indeterminate". A favorable clinical response is "cure".

Table 7 Composite Microbiological and Clinical Response Definitions at the TOC Visit

Outcome	Definition
Cure	By-subject microbiological response was microbiological success and the clinical response was clinical cure.
Failure	By-subject microbiological response was microbiological failure or the clinical response was clinical failure.
Indeterminate	By-subject microbiological response was indeterminate and/or the clinical response was indeterminate.

7.1.3.6 Blood sampling for Hematology, Coagulation Chemistry, and Urine sampling for urinalysis

Obtain blood samples for hematology, coagulation and chemistry, and urine samples for urinalysis listed in Table 8 at the visits specified in the flow chart (Section 6.0) and send the samples to the central laboratory designated by the Sponsor. Serum creatinine (for the monitoring of CrCl) and urine hCG (ensure negative before randomization in females of child bearing potential) test are performed in each investigational institution but not in the central laboratory. At screening, local laboratory data is used for enrollment criteria of laboratory test but the blood/urine samples for Hematology, Coagulation and Chemistry test, and urinalysis of baseline are collected separately, and sent to a central laboratory.

Table 8 The List of Laboratory Tests

Hematology	Chemistry	Urinalysis
Red blood cell count (RBC)	Total protein	Nitrite
Hemoglobin	Albumin	Leukocyte esterase
Hematocrit	Total bilirubin	Urine pregnancy test (urine hCG) †
White blood cell count (WBC)	Aspartate aminotransferase (AST)	
WBC differential (neutrophil, eosinophil, basophil, lymphocyte, monocyte)	Alanine aminotransferase (ALT)	
	Alkaline phosphatase	
	Blood urea nitrogen	
Platelet count	Sodium	
Prothrombin time	Potassium	
Direct Coombs test	non-fasting serum glucose	
	Serum creatinine†	
	C-reactive protein (CRP)	
† Test is performed locally in each investigational institution.		

7.1.3.7 Assessment of creatinine clearance

During this study period, serum creatinine value to determine dose adjustment will be collected in the local laboratory. Obtain serum creatinine value and estimate the subject's CrCl using the subject's serum creatinine value, actual body weight, and the appropriate Cockroft-Gault formula described in Section 5.2.1.1. For patients with changing renal function (creatinine clearance is either close to 30 or close to 50 mL/min) while on study therapy, obtain serum creatinine value and monitor CrCl at least daily and adjust the dosage of MK-7625A accordingly. Obtained serum creatinine value should be recorded in the eCRF.

7.1.3.8 Urine pregnancy test (females of child bearing potential)

Obtain urine sample for serum pregnancy test (women of child bearing potential and those who are less than 1 years postmenopausal only) to be assessed at the study sites (ensure that the test is negative before randomization).

7.1.3.9 Pharmacokinetic Evaluations

The decision as to which plasma samples collected will be assayed for evaluation of pharmacokinetics will be collaboratively determined by the Departments of Drug Metabolism and the other appropriate department. The collected sparse pharmacokinetic samples will be included in a future cross study POP-PK analysis.

7.1.3.9.1 Blood Collection for Pharmacokinetics

Blood for pharmacokinetic analysis will be collected from all subjects who received MK-7625A (approximately 115). Table 9 shows the time points of blood collection.

Sample collection, storage and shipment instructions for plasma samples will be provided in a separate Operation/Laboratory Manual.

Table 9 Blood Sampling Points for PK

	pre-treatment (15 minutes prior to infusion)	just before the completion of infusion	30-90 minutes after the completion of infusion	2.5-3.5 hours after the completion of infusion	5.5-7 hours after the completion of infusion
Day 1	X†				
Day 3 [allowance: +2 days (Day 4 or Day 5)]	X	X	X‡	X‡	X‡

X: Collection of specimen
† A sample will be collected before initial administration of study drug.
‡ When sample collection of five points will be difficult, the sample of at least one point will be collected among the latter three points.

7.1.3.10 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the Laboratory Manual.

7.1.3.11 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of Future Biomedical Research:

- DNA for future research.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final trial visit 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.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

7.1.4.2 Blinding/Unblinding

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

7.1.4.3 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

- Clinical testing equipment relevant to inclusion/exclusion criteria and clinical evaluation.

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 (Visit 1)

Baseline (screening) assessments are to be performed as close as possible to the start of study therapy and at most within 1 day before the start of administration of the first dose of MK-7625A. Potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. All baseline assessment results except the results of the urine culture must be available before registration of this study.

7.1.5.2 Treatment Period (Visit 2-9)

For study Day 2 through 7 all study assessments are recommended to be performed at a approximately consistent time of day for the study patient (e.g. every morning) for each calendar day. End-of-therapy assessments are to be performed within 1 day after completion of administration of the last dose of study drug.

7.1.5.3 Follow-up Period (Visit 10 and 11)

Test-of-cure visit assessments are to be performed 7 days (± 2 days) after completion of administration of the last dose of study drug. Subjects will be required to return to the investigational institution at 28 to 35 days after the last dose of MK-7625A for post-trial visits.

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 LFU visit, 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 MK-7625A 3 g/dose or 9 g/day.

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 serious adverse event, even if no other seriousness 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 Event of Clinical Interest (ECI), 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 LFU visit 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. Therefore, these events are considered serious by the Sponsor for collection purposes.

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

Refer to Table 10 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 LFU visit, 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 LFU visit, 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 overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. 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).

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 10. The investigator's assessment of causality is required for each adverse event. Refer to Table 10 for instructions in evaluating adverse events.

Table 10 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; 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	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a 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	
	†**Is a congenital anomaly/birth defect (**in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events 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 †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	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 **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; 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:	
	Exposure	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?
	Time Course	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)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)**	
	Dechallenge	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.)
	Rechallenge	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.
	Consistency with Trial Treatment Profile	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.		
Record one of the following:	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	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.	
No, there is not a reasonable possibility of Sponsor's product relationship	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 trial. Changes to analyses made after the protocol has been finalized, but prior to data base lock, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2-8.12.

Study Design Overview	A Multicenter, Open-label, Noncomparative, Japanese Phase III Study to Assess the Efficacy and Safety of Ceftolozane/Tazobactam (MK-7625A) in Japanese Patients with Uncomplicated Pyelonephritis and Complicated Urinary Tract Infection
Treatment Assignment	Non-randomized, open-label and single arm
Analysis Populations	Efficacy: Microbiologically Evaluable (ME), Clinical Evaluable (CE) and microbiological modified intent-to-treat (mMITT) Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	Per-subject microbiological response at TOC
Secondary Endpoints	Per-subject microbiological response at EOT and LFU Per-pathogen microbiological response at EOT, TOC, and LFU Clinical response at EOT, TOC, and LFU Composite (clinical and microbiological) response at TOC
Statistical Methods for Key Efficacy Analyses	For the primary and secondary efficacy endpoints, point estimate and two-sided 95% confidence intervals of response rate will be calculated using the Clopper-Pearson method.
Statistical Methods for Key Safety Analyses	All adverse events will be tabulated. The 95% confidence interval will be provided using the Clopper-Pearson method for key safety endpoints. Summary statistics for baseline, on-treatment, and change from baseline values will be provided for the continuous measures such as laboratory, and vital signs parameters.
Interim Analyses	No interim analyses are planned for this trial.
Multiplicity	No multiplicity adjustment is planned for the trial.
Sample Size and Power	This trial will enroll 115 subjects to receive MK-7625A, and will allow estimation of the microbiological response rate at TOC among subjects receiving MK-7625A in the ME population with a 95% confidence interval of (75.0%, 92.3%). This is based on the following assumptions: 1) an approximate 35% dropout and/or protocol deviation rate excluding subjects from the ME population, and 2) an observed response rate of 85.1% in the MK-7625A group.

8.2 Responsibility for Analyses/In-House Blinding

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

This trial is being conducted as a non-randomized, open-label trial, i.e., subjects, investigators, and Sponsor personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned.

The Clinical Biostatistics department will generate the allocation schedule(s) for study treatment assignment.

8.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0.

8.4 Analysis Endpoints

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

8.4.1 Efficacy Endpoints

The primary efficacy endpoint is microbiological response rate at TOC, defined as the proportion of subjects in the analysis population who have an overall outcome of microbiological eradication at TOC. For subjects with more than 1 uropathogen isolated at baseline, an overall outcome of microbiological eradication will be based on eradication of all baseline uropathogens.

The secondary efficacy endpoints include:

- Per-subject microbiological response rate at EOT and LFU.
- Per-pathogen microbiological response rate at EOT, TOC and LFU, defined as the proportion of subjects in the analysis population who have an outcome of microbiological eradication for each uropathogen isolated at baseline.
- Clinical response rate at EOT, TOC and LFU, defined as the proportion of subjects in the analysis population who have a response of clinical cure.
- Composite (clinical and microbiological) response at TOC, defined as the proportion of subjects in the analysis who have an overall outcome of microbiological eradication and the response of clinical cure at TOC.

8.4.2 Safety Endpoints

An initial description of the safety measures is included in Sections 4.2.3.2.

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

The microbiological modified intent-to-treat (mMITT) population consists of all allocated subjects who receive at least one dose of study treatment and have at least 1 acceptable causative uropathogen from a baseline urine specimen ($\geq 10^5$ CFU/mL).

The clinically evaluable (CE) population will be a subset of the mMITT population who adhere to study procedures and have a clinical response at the visit interest within the specified visit window. All subjects in the CE population have to have an evaluable clinical outcome; an indeterminate response is excluded from this population.

The microbiologically evaluable (ME) population will be a subset of the CE population who have an appropriately collected urine culture specimen and interpretable urine culture result at the visit interest.

The ME population will serve as the primary population for the analysis of the microbiological response and composite endpoints in this trial. In addition, the CE population will serve as the primary population for the analysis of the clinical response endpoints.

A supportive analysis using the mMITT population will be performed for the primary and secondary endpoints.

The final determination on major protocol deviations, and thereby the composition of the ME, CE and mMITT populations, will be made prior to the final database lock and will be documented in a separate memo.

Details on the approach to handling missing data are provided in Section 8.6 Statistical Methods.

8.5.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this trial. The ASaT population consists of all allocated subjects who received at least one dose of study treatment.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling missing data for safety analyses are provided in Section 8.6 Statistical Methods.

8.6 Statistical Methods

8.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the sSAP.

For the primary efficacy endpoint of per-subject microbiological response rate at TOC, the point estimate and two-sided 95% confidence intervals of response rate will be calculated using the Clopper-Pearson method.

For the secondary endpoints, the same method will be applied as primary endpoint.

For microbiological, clinical and composite responses, missing data will be primarily handled with a treatment failure approach for the mMITT populations and a data-as-observed approach for the ME or CE population which is defined as follows:

- For analyses of clinical response and microbiological response, including the composite response, in the mMITT population, the subjects with a missing clinical response or microbiological response (e.g., indeterminate) will be categorized as treatment failures.

- For the analyses in the ME or CE population, the subjects with a missing clinical response or microbiological response (e.g., including indeterminate) will be excluded from the population.

- A missing per-pathogen microbiological outcome at the TOC visit will be considered an indeterminate outcome unless the per-pathogen microbiological outcome at EOT is persistence. A per-pathogen microbiological outcome of persistence at EOT will be carried forward to the TOC visit.

- A missing per-pathogen microbiological outcome at the LFU visit will be considered an indeterminate outcome unless the per-pathogen microbiological outcome at TOC is persistence. A per-pathogen microbiological outcome of persistence at TOC will be carried forward to the LFU visit.

- A missing clinical outcome at the TOC visit will be considered an indeterminate outcome unless the clinical outcome at EOT is failure. A clinical response of failure at EOT will be carried forward to the TOC visit.

- A missing clinical outcome at the LFU visit will be considered an indeterminate outcome unless the clinical outcome at TOC is failure. A clinical response of failure at TOC will be carried forward to the LFU visit.

Table 11 summarizes the key efficacy analyses.

Table 11 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint				
Per-subject microbiological response rate at TOC	P	Clopper-Pearson method	ME	Data As Observed
Secondary Endpoints				
Per-subject microbiological response rate at TOC	S	Clopper-Pearson method	mMITT	Treatment Failure Approach
Per-subject microbiological response rate at EOT and LFU	P	Clopper-Pearson method	ME	Data As Observed
Per-subject microbiological response rate at EOT and LFU	S	Clopper-Pearson method	mMITT	Treatment Failure Approach
Per-pathogen microbiological response rate at EOT, and TOC and LFU	P	Clopper-Pearson method	ME	Data As Observed
Per-pathogen microbiological response rate at EOT, TOC, and LFU	S	Clopper-Pearson method	mMITT	Treatment Failure Approach
Clinical response rate at EOT, TOC and LFU	P	Clopper-Pearson method	CE	Data As Observed
Clinical response rate at EOT, TOC, and LFU	S	Clopper-Pearson method	mMITT	Treatment Failure Approach
Composite (clinical and microbiological) response rate at TOC	P	Clopper-Pearson method	ME	Data As Observed
Composite (clinical and microbiological) response rate at TOC	S	Clopper-Pearson method	mMITT	Treatment Failure Approach

† P=Primary approach; S=Supportive approach.

8.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events (AEs), laboratory tests and vital signs measurements.

To address the primary objective of safety and tolerability, all adverse events (preferred terms as well as system organ class terms) will be tabulated.

In addition, the broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, a drug related AE, a serious AE, and an AE which is both drug-related and serious, and who discontinued the study drug due to an AE will be considered as key safety endpoints. The 95% confidence interval will be provided using the Clopper-Pearson method for key safety endpoints.

Summary statistics for baseline, on-treatment, and change from baseline values will be provided for the continuous measures such as laboratory and vital signs parameters.

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

8.6.3.1 Demographic and Baseline Characteristics

The number and percentage of subjects screened, enrolled, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables.

8.6.3.2 Population PK Analyses

For the plasma concentration data of ceftolozane, tazobactam and tazobactam M1, summary statistics will be provided.

Based on the plasma concentration data obtained within this trial, a separate population Pharmacokinetics (PK) analysis will be performed. The prospective details of this analysis will be specified in a separate population PK analysis plan.

8.7 Interim Analyses

No interim analyses are planned for this trial.

8.8 Multiplicity

No multiplicity adjustment is planned for the trial.

8.9 Sample Size and Power Calculations

8.9.1 Sample Size and Power for Efficacy Analyses

This is an estimation study. This study will enroll 115 subjects to receive MK-7625A (the rationale for the enrollment of 115 subject is referred to Section 4.2.1), and will allow estimation of the per-subject microbiological response rate at TOC among subjects receiving MK-7625A in the ME population with a 95% confidence interval of (75.0%, 92.3%). This is based on the following assumptions: 1) an approximately 35% dropout and/or protocol deviation rate excluding subjects from the ME population, 2) an observed response rate of 85.1% in the MK-7625A group based on the study results conducted outside of Japan (from protocol CXA-cUTI-10-04 and CXA-cUTI-10-05). The calculation is based on the exact binomial method proposed by Clopper and Pearson with 74 subjects in MK-7625A expected to be included in the analysis, and is carried out using PASS2008. Table 12 summarizes estimates of the confidence interval for the MK-7625A group under various assumptions.

Table 12 Confidence Interval for MK-7625A Under Various Assumption With 74 Evaluable Subjects in ME Population

Number of Subjects with a eradication response	Estimate of Response Rate	95% Confidence Interval
55	74.3%	(62.8%, 83.8%)
59	79.7%	(68.8%, 88.2%)
63	85.1%	(75.0%, 92.3%)
67	90.5%	(81.5%, 96.1%)
71	95.9%	(88.6%, 99.2%)

8.10 Subgroup Analyses and Effect of Baseline Factors

To determine whether the response rate is consistent across various subgroups, the response rate in the ME at TOC population for the primary endpoints will be estimated within each category of each subgroup. The following are classification variables:

- Baseline diagnosis (pyelonephritis vs. cLUTI)
- CrCl (≤50 mL/min, >50 mL/min)
- Age categories (≥18 to <45 years, ≥45 to <65 years, ≥65 years)
- ESBL status of Enterobacteriaceae
- Presence of bacteremia at baseline
- Subject with/without indwelling catheter
- Subject with/without complicated factors for pyelonephritis
- Number of uropathogens present at baseline

The consistency of the response rate will be assessed descriptively via summary statistics by category for the classification variables listed above.

8.11 Compliance (Medication Adherence)

Drug accountability data for MK-7625A will be collected during the study. These results will be used to calculate subject compliance.

For each subject, percent compliance will then be calculated using the following formula:

Compliance (%) = 100 times (Actual Number of Doses on Therapy) / (Total Number of Expected Doses on Therapy).

For a subject who is followed for the entire study period, the "Total Number of Expected Doses on Therapy" is 21. For a subject who discontinued from the study permanently, the "Total Number of Expected Doses on Therapy" is the total scheduled number of doses from allocation to the date of the last dose of study medication. Compliance (%) will be categorized as: < 80%, ≥ 80% to ≤ 120%, and > 120%.

Summaries of percent compliance and compliance (%) categories will be provided for the ME at TOC population.

8.12 Extent of Exposure

The extent of exposure to study treatment will be evaluated by summary statistics (n, mean, median, standard deviation, minimum, and maximum) and frequencies [1 to 4 days, 5 to 6 days, 7 days and >7 days] for the "Number of Days on Therapy", and frequencies [by 3 doses] for the "Number of Does on Therapy" for ASaT 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 13.

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 13 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
MK-7625A 1.5 g (ceftolozane 1 g/tazobactam 0.5 g)	Lyophilized Powder for I.V. infusion	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.

Investigator will receive open label vials of MK-7625A.

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 (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.

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 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 Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. 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 FDAMA/FDAAA 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 FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

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 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

1. Takeda S, Ishii Y, Hatano K, Tateda K, Yamaguchi K. Stability of FR264205 against AmpC β- lactamase of Pseudomonas aeruginosa. Int J Antimicrob Agents. 2007; 30(5):443-45.
2. Takeda S, Nakai T, Wakai Y, Ikeda F, Hatano K. In vitro and in vivo activities of a new cephalosporin, FR264205, against Pseudomonas aeruginosa. Antimicrob Agents Chemother. 2007; 51(3):826-30.
3. Wagenlehner FME, Naber KG. Current challenges in the treatment of complicated urinary tract infections and prostatitis. Clin Microb Infect 2006;12(S3):67-80.
4. Nicolle LE, AMMI Canada Guidelines Committee. Complicated urinary tract infection in adults. Can J Infect Dis Med Microbiol 2005; 16 (6): 349-60.
5. The Japanese Association for Infectious Diseases/ Japanese Society of Chemothrapy. Guideline on Use of Antibiotics 2005: 186-92.
6. Ishikawa K, Hamasuna R, Uehara S, Yasuda M, Yamamoto S, Hayami H, et al. Japanese nationwide surveillance in 2011 of antibacterial susceptibility patterns of clinical isolates from complicated urinary tract infection cases. J Infect Chemother. 2015: 1-11.
7. Ministry of Health, Labour and Welfare. Japan Nosocomial Infections Surveillance (Annual report January to December 2013).
8. Lancefield RC, A serological differentiation of human and other groups of hemolytic streptococci. J Exp Med 1933; 57: 571-95.

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 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.11 – Future Biomedical Research Sample Collection will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by the Sponsor focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of subject consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com) and a form will be provided to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. Documentation will be sent to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject’s personal information and their specimens. In this situation, the request for specimen destruction can not be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards (e.g., ISO17799) to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Subjects

No information obtained from exploratory laboratory studies will be reported to the subject, family, or physicians. Principle reasons not to inform or return results to the subject include: Lack of relevance to subject health, limitations of predictive capability, and concerns regarding misinterpretation.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information. After the clinical trial has completed, if any exploratory results are definitively associated with clinical significance, the Sponsor will endeavor to make such results available through appropriate mechanisms (e.g., scientific publications and/or presentations). Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all subjects diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. No additional risks to the subject have been identified as no additional specimens are being collected for Future Biomedical Research (i.e., only leftover samples are being retained).

The Sponsor has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

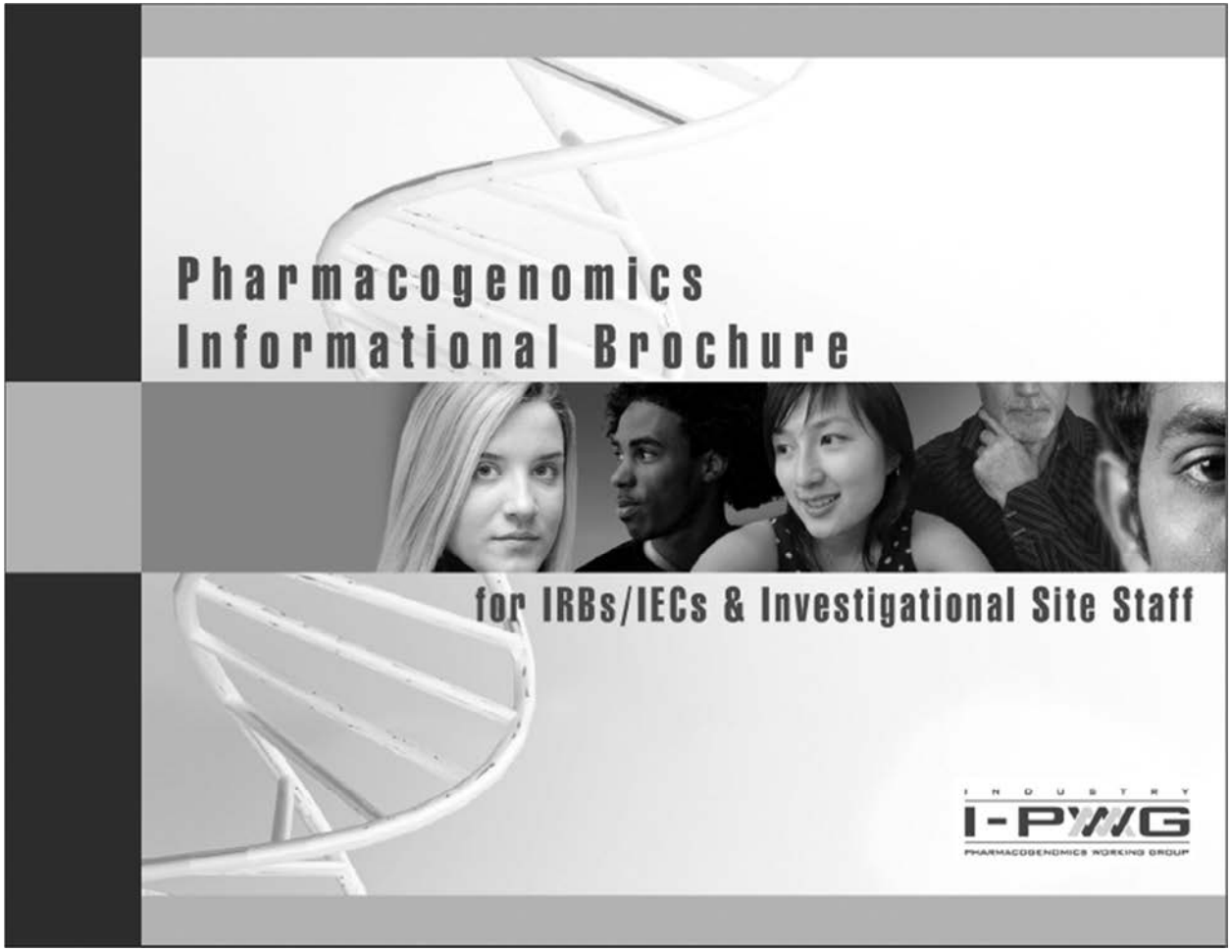
12. Questions

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

12.3 Pharmacogenetics Informational Brochure for IRBs/IECs & Investigational Site Staff



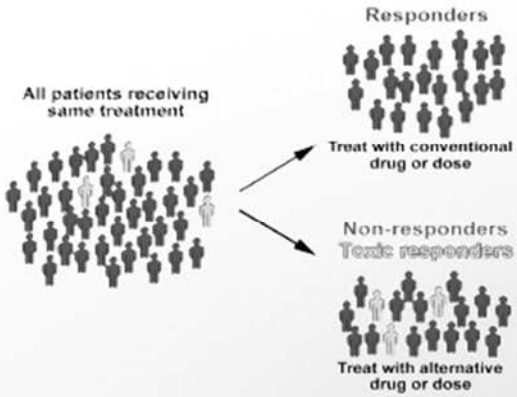
This Informational Brochure is intended for IRBs/IECs & Investigational Site Staff. The brochure was developed to address issues relevant to DNA collection and research in the context of pharmaceutical drug development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

What is DNA and What is Pharmacogenomics?

The cells of the body contain **deoxyribonucleic acid** (**DNA**). DNA is inherited, and carries a code (in the form of **genes**), which determines physical appearance and other personal features. In a process called gene transcription, DNA is copied into a related molecule, ribonucleic acid (RNA), before ultimately being translated into proteins, which determine cellular function. Naturally-occurring variation in DNA is a major determinant of differences among people. This variation, referred to as **genetic polymorphism**, occurs both within genes and outside of genes throughout the entire **human genome**. This variation partly explains why some people develop certain diseases and others do not, why some people respond better than others to certain drugs, and why some people develop side effects while others do not.

Pharmacogenomics (PGx) is a branch of science that uses genetic/genomic information to better understand why people respond differently to drugs. The terms **pharmacogenomics** and **pharmacogenetics** are often used interchangeably, although pharmacogenetics generally refers to the study of DNA, while pharmacogenomics is a broader term encompassing the study of both DNA and RNA[1], and generally on a larger scale. Pharmacogenomic research is different from **genetic testing** done for the purpose of diagnosing a person with a certain disease or for risk for developing a certain disease (e.g., genetic testing for Huntington's Disease). PGx focuses on genetic variability that affects response to drugs. This primarily occurs through pathways related to drug metabolism, drug mechanism of action, disease etiology or subtype, and adverse events. PGx overlaps with **disease genetics** research since different disease subtypes can respond differently to drugs.



Why is Pharmacogenomics Important?

PGx is one approach to explore whether a drug will be useful or harmful in certain people. By identifying genetic polymorphisms that are associated with drug efficacy and safety, PGx is allowing for more individualized drug therapies based on the genetic makeup of patients. This is sometimes referred to as **personalized medicine**. By better understanding diseases at the molecular level, PGx is opening opportunities for the discovery of novel drugs.

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PGx has the overarching goal of developing safer, more effective drugs, and ensuring that patients receive the correct dose of the correct drug at the correct time.

How is Pharmacogenomics Being Used in Drug Development?

PGx is increasingly becoming a core component of drug development programs. By using PGx to determine how drugs work differently in subgroups of patients, drug developers are making better decisions about which drugs to develop and how best to develop them. Technologies are now available to simultaneously analyze over 1 million genetic polymorphisms in the human genome. This is allowing for the identification of novel genetic markers of drug response and of disease in absence of pre-existing knowledge of the involvement of specific pathways.

PGx research is currently being used in drug development to:

- Explain variability in response among subjects in clinical trials
- Address emerging clinical issues, such as unexpected adverse events
- Determine eligibility for clinical trials (pre-screening) to optimize trial design
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of adverse events
- Better understand the mechanism of action or metabolism of new and existing drugs
- Provide better understanding of disease mechanisms
- Allow physicians to prescribe the right drugs at the optimal dose for individual patients

2

Pharmacogenomics Already a Reality in Drug Labels

A number of drugs now have instructions on their labels either recommending or requiring a PGx test when prescribing a drug or when making dosing decisions. A well-known example is the anti-coagulant drug *warfarin*. The drug label for warfarin now includes a recommended PGx test to minimize the risk of excessive bleeding (US label). There are currently three categories of PGx information in drug labels according to the FDA:

i) tests **required** for prescribing

ii) tests **recommended** when prescribing

iii) PGx information **for information only**.

For a current list of examples of how PGx is impacting drug labeling see:

www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

DNA Samples from Clinical Trials An Invaluable Resource

Adequate sample sizes and high-quality clinical data are key to advancements in the field of PGx. Drug development programs are therefore an invaluable resource and a unique opportunity for highly productive research in PGx. Although PGx is a rapidly evolving branch of science, the complexities of the genetic code are only beginning to be understood. As scientific discoveries continue to be made, samples collected today will become a valuable resource

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for future research. This may lead to the future development of new drugs that are better targeted to certain individuals and to disease subtypes.

For these reasons, it is vital to systematically collect DNA samples across all centers recruiting subjects into clinical trials that include a PGx component (where local regulations permit). Consent for storage of samples for future research should also be obtained if maximum benefit is to be derived from DNA samples donated by subjects. The scope of the research that may be performed both during the trial and in the future should be clearly defined in the informed consent form.

Informed Consent

Policies and regulations for legally effective informed consent vary on national, state, and local levels. There currently are no internationally recognized regulations that dictate the basic elements of informed consent for PGx research. The I-PWG has published an article on the elements of informed consent to be considered in PGx research studies[2]. These elements build upon existing basic elements of informed consent for clinical research on human subjects[3].

Return of Genomic Research Results to Study Subjects

Policies for the return of genomic results to study subjects vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of PGx research results to study subjects. These include i) the conditions under which genomic results were generated (i.e., research laboratory environment versus accredited diagnostic laboratory), ii) whether the results will have an impact on patient medical care, iii) whether genetic counseling is necessary, and iv) international, national, and local guidelines, policies, legislation, and regulations regarding subjects' rights to access data generated on them. These considerations are addressed in detail in Renegar et al. 2006[4].

Privacy, Confidentiality, and Patient Rights

An issue that is generally perceived to be of relevance to clinical genetic research is the risk associated with inadvertent or intentional disclosure and misuse of genetic data. Although coded specimens generally have been considered adequate to protect patient privacy in most clinical development, companies and other institutions involved in PGx research have historically applied a variety of additional safeguards that can be used alone, or in combination, to further minimize the potential risk of disclosure and misuse of genetic data. These include:

i) Sample Labeling

DNA samples and corresponding clinical data can be labeled in several ways to achieve different levels of patient privacy and confidentiality. Definitions of labeling methods are provided in the glossary and are described in greater detail in the ICH Guidance E15[1]. It is important to recognize that there is a trade-off between the level of patient privacy protection and the ability to perform actions related to withdrawal of consent, data return, clinical monitoring, subject follow-up, and addition of new data (see Table 1)[1]. The *Identified* and *Anonymous* labeling categories described in the table are generally not applicable to pharmaceutical clinical trials.

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Table adapted from ICH Guidance E15

Sample Coding Category		Link Between Subject's Personal Identifiers and Genomic Biomarker Data	Traceability back to the Subject (Actions Possible, Including e.g., Sample Withdrawal or Return of Individual Genomic Results at Subject's Request	Ability to Perform Clinical Monitoring, Subject Follow-up, or Addition of New Data	Extent of Subject's Confidentiality and Privacy Protection
Identified		Yes (Direct) Allows for Subjects to be Identified	Yes	Yes	Similar to General Healthcare Confidentiality and Privacy
Coded	Single	Yes (Indirectly) Allows for Subjects to be Identified (via Single, Specific Coding Key)	Yes	Yes	Standard for Clinical Research
	Double	Yes (Very Indirectly) Allows for Subjects to be Identified (via the Two Specific Coding Keys)	Yes	Yes	Added Privacy and Confidentiality Protection over Single Code
Anonymized		No Does not Allow Subject to be Re-Identified as the Coding-Key(s) Have Been Deleted	No	No	Genomic Data and Samples no Longer Linked to Subject as Coding Key(s) have been Deleted
Anonymous		No – Identifiers Never Collected and Coding Keys Never Applied. Does not Allow for Subjects to be Identified	No	No	Genomic Data and Samples Never Linked to Subject

ii) Separation of Data and Restricted Access

- Maintaining PGx-related documentation separate from other medical records.
- Restricting access to data and samples by means of password-protected databases and locked sample storage facilities.

PGx studies in pharmaceutical development are generally conducted in research laboratories that are not accredited diagnostic laboratories. Therefore, PGx research data usually cannot be used to make clinically meaningful or reliable decisions about a subject's health or health risks. Furthermore, confidentiality protections described above serve to guard against inappropriate disclosure of these data. For these reasons, the potential risk to a subject's employment or health/life insurance is considered to be minimal. The measures taken to protect subjects against reasonably foreseeable risks should be addressed in the informed consent form[2].

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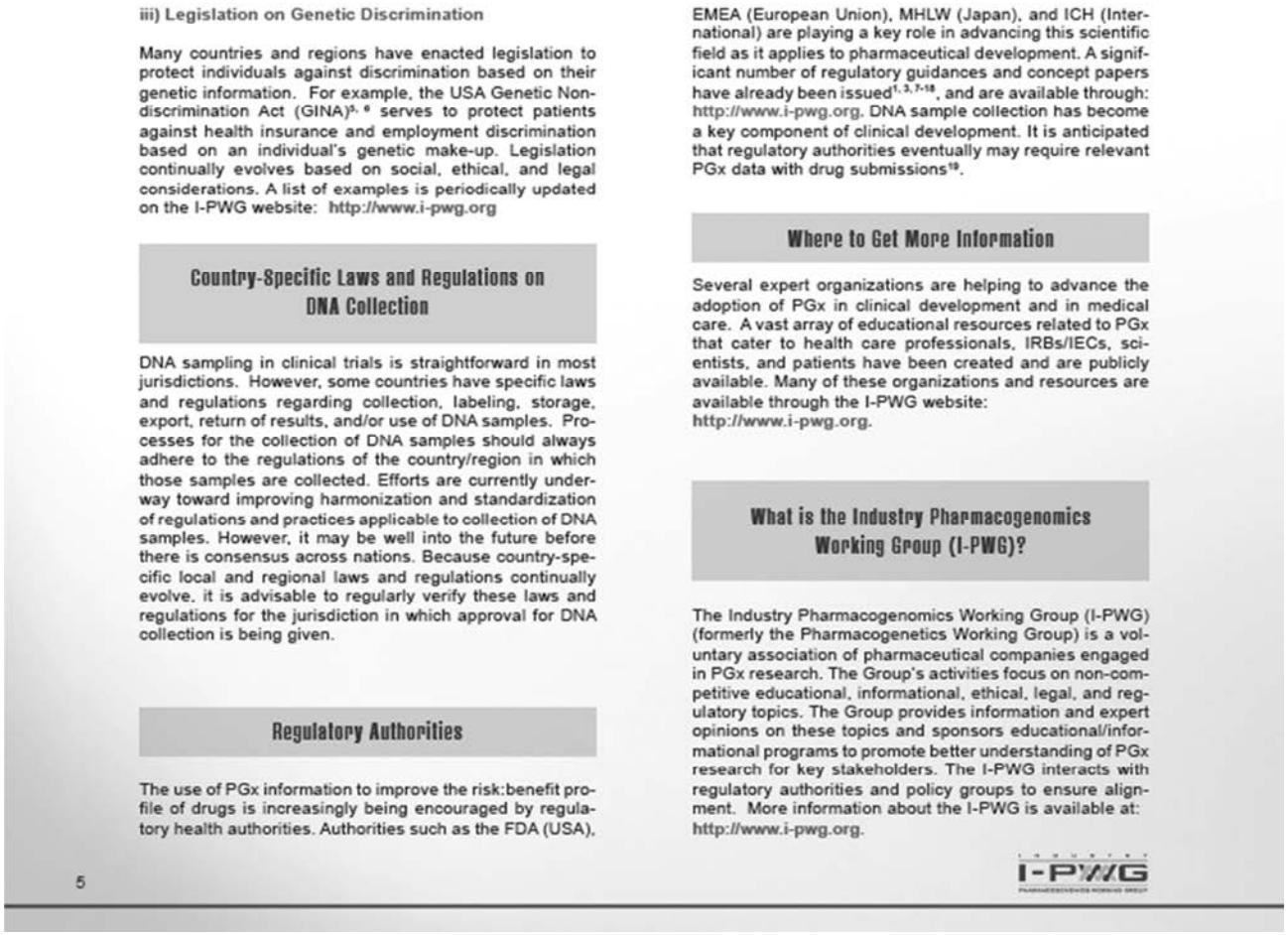

iii) Legislation on Genetic Discrimination

Many countries and regions have enacted legislation to protect individuals against discrimination based on their genetic information. For example, the USA Genetic Non-discrimination Act (GINA)[5, 6] serves to protect patients against health insurance and employment discrimination based on an individual's genetic make-up. Legislation continually evolves based on social, ethical, and legal considerations. A list of examples is periodically updated on the I-PWG website: http://www.i-pwg.org

Country-Specific Laws and Regulations on DNA Collection

DNA sampling in clinical trials is straightforward in most jurisdictions. However, some countries have specific laws and regulations regarding collection, labeling, storage, export, return of results, and/or use of DNA samples. Processes for the collection of DNA samples should always adhere to the regulations of the country/region in which those samples are collected. Efforts are currently underway toward improving harmonization and standardization of regulations and practices applicable to collection of DNA samples. However, it may be well into the future before there is consensus across nations. Because country-specific local and regional laws and regulations continually evolve, it is advisable to regularly verify these laws and regulations for the jurisdiction in which approval for DNA collection is being given.

Regulatory Authorities

The use of PGx information to improve the risk:benefit profile of drugs is increasingly being encouraged by regulatory health authorities. Authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development. A significant number of regulatory guidances and concept papers have already been issued[1, 3, 7-18], and are available through: http://www.i-pwg.org. DNA sample collection has become a key component of clinical development. It is anticipated that regulatory authorities eventually may require relevant PGx data with drug submissions[19].

Where to Get More Information

Several expert organizations are helping to advance the adoption of PGx in clinical development and in medical care. A vast array of educational resources related to PGx that cater to health care professionals, IRBs/IECs, scientists, and patients have been created and are publicly available. Many of these organizations and resources are available through the I-PWG website: http://www.i-pwg.org.

What is the Industry Pharmacogenomics Working Group (I-PWG)?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in PGx research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of PGx research for key stakeholders. The I-PWG interacts with regulatory authorities and policy groups to ensure alignment. More information about the I-PWG is available at: http://www.i-pwg.org.

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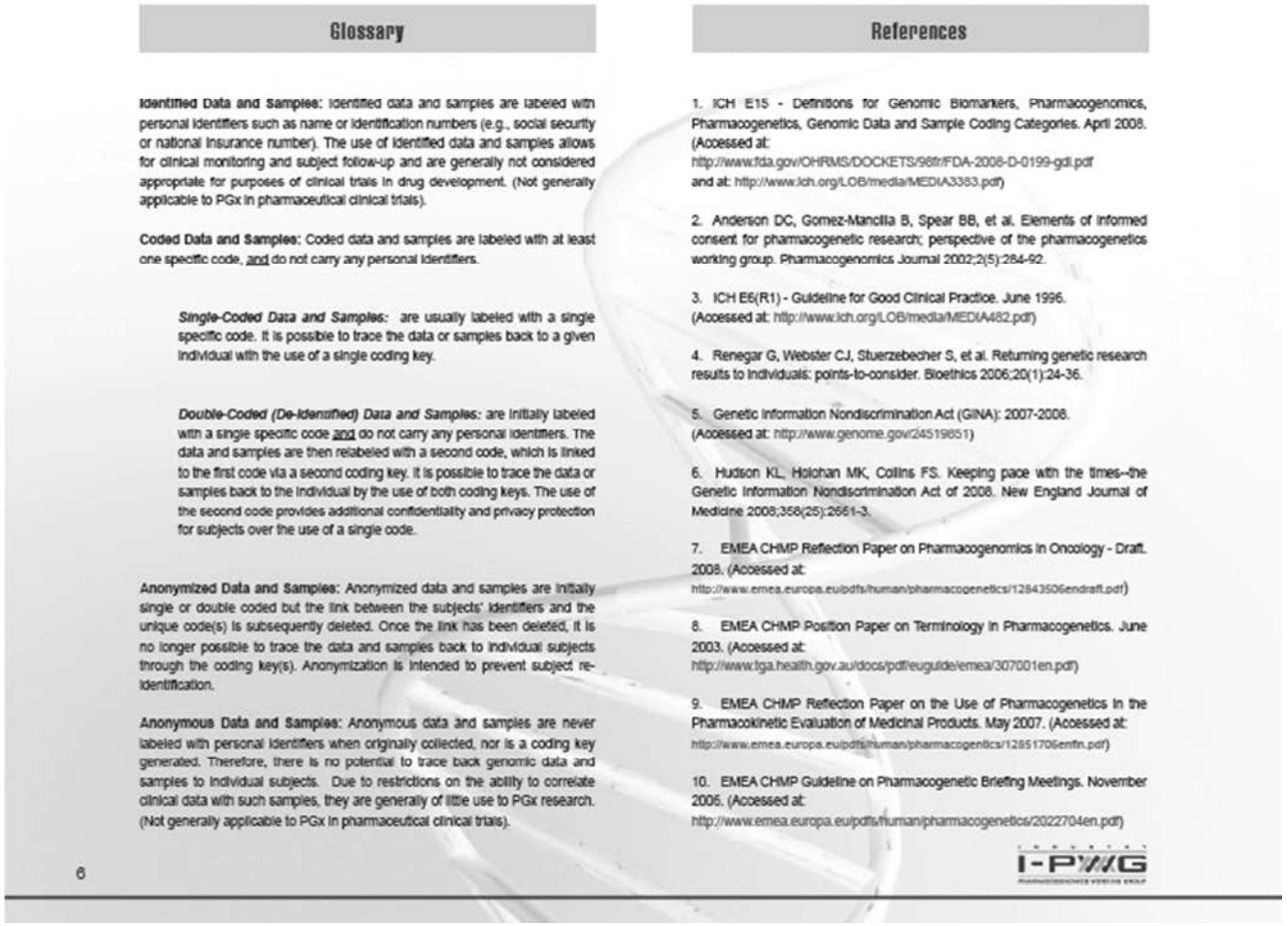

Glossary

Identified Data and Samples: Identified data and samples are labeled with personal identifiers such as name or identification numbers (e.g., social security or national insurance number). The use of identified data and samples allows for clinical monitoring and subject follow-up and are generally not considered appropriate for purposes of clinical trials in drug development. (Not generally applicable to PGx in pharmaceutical clinical trials).

Coded Data and Samples: Coded data and samples are labeled with at least one specific code, and do not carry any personal identifiers.

Single-Coded Data and Samples: are usually labeled with a single specific code. It is possible to trace the data or samples back to a given individual with the use of a single coding key.

Double-Coded (De-identified) Data and Samples: are initially labeled with a single specific code and do not carry any personal identifiers. The data and samples are then relabeled with a second code, which is linked to the first code via a second coding key. It is possible to trace the data or samples back to the individual by the use of both coding keys. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code.

Anonymized Data and Samples: Anonymized data and samples are initially single or double coded but the link between the subjects' identifiers and the unique code(s) is subsequently deleted. Once the link has been deleted, it is no longer possible to trace the data and samples back to individual subjects through the coding key(s). Anonymization is intended to prevent subject re-identification.

Anonymous Data and Samples: Anonymous data and samples are never labeled with personal identifiers when originally collected, nor is a coding key generated. Therefore, there is no potential to trace back genomic data and samples to individual subjects. Due to restrictions on the ability to correlate clinical data with such samples, they are generally of little use to PGx research. (Not generally applicable to PGx in pharmaceutical clinical trials).

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12.4 Approximate Blood Volumes Drawn by Trial Visit and by Sample Types

Approximate blood volume is shown in the table below. There is a possibility to be different volume by subject's condition etc.

	Screening	Treatment					Follow-up	
Trial Visit:	1	2	3	4	5-8	9	10	11
Blood Parameter	Approximate Blood Volume (mL)							
Hematology	2.0			2.0		2.0	2.0	2.0
Coagulation	1.8			1.8		1.8	1.8	1.8
Serum Chemistry	3.0			3.0		3.0	3.0	3.0
Coombs	2.0					2.0		
Glucose	2.0			2.0		2.0	2.0	2.0
Serum creatinine†	1.0	1.0	1.0	1.0				
Culture for blood sample†	20.0‡							
Hematology†	2.0							
Chemistry†	2.0							
Blood for Genetic Analysis		8.5						
Collection of sample to measure MK-7625A plasma concentration		2.0		10.0				
Expected Total (mL)	35.8	11.5	1.0	19.8		10.8	8.8	8.8

† Test is performed locally in each investigational institution.

‡ Culture for blood sample is conducted as indicated in subjects who present with clinical signs and/or symptoms of pyelonephritis or bacteremia (OR subjects with indwelling catheters whose baseline urine specimen are obtained through the catheter).

12.5 Clinical Study Conduct System

Clinical study conduct system is shown in attachment 1 and 2.

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	