

Title: A Phase II, Randomized, Active Comparator-Controlled Clinical Trial to Study the Safety, Tolerability, and Efficacy of MK-7655 + Imipenem/Cilastatin versus Imipenem/Cilastatin Alone in Patients with Complicated Urinary Tract Infection. Protocol Number: MK-7655-003

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Sponsor: Merck Sharp & Dohme Corp., (a subsidiary of Merck & Co. Inc.)

Purpose of Research

The goal of this research is to test the safety and effectiveness of the study drug, MK-7655 when it is given with Imipenem/Cilastatin.

MK-7655 is an experimental drug that has not been approved by the U.S. Food and Drug Administration (FDA) for sale by prescription. MK-7655 works by blocking an enzyme made by certain bacteria that can degrade Imipenem/Cilastatin. It has been developed by Merck for use in combination with Imipenem/Cilastatin (licensed as PRIMAXIN®/TIENAM®) for the possible treatment of infections caused by bacteria. It has been tested in animals and in well people. It is still being tested in people with bacterial infections.

Since no one knows yet whether the experimental drug, MK-7655, will be effective or not, not everyone in the research study will be treated with MK-7655.

There are three groups in this study. Each group will get an antibiotic called Imipenem/Cilastatin which treats most infections in the urine caused by bacteria. Two of the groups get different amounts (doses) of MK-7655. One group will not receive the drug being tested.

Group 1 will receive MK-7655 (250 mg) + Imipenem/Cilastatin.

Group 2 will receive MK-7655 (125 mg) + Imipenem/Cilastatin.

Group 3 will receive Placebo + Imipenem/Cilastatin.

The study drug, MK-7655 or placebo, and Imipenem/Cilastatin will be given at the same time for a minimum of 4 days.

Inclusion Criteria:

1. Participant has been domiciled in a health care facility (e.g., hospital, nursing home) for at least 48 hours within the preceding 90 calendar days.
2. Clinically suspected and/or bacteriologically documented cUTI or acute pyelonephritis judged by the investigator to be serious (requiring hospitalization and treatment with IV antibiotic therapy).
3. Pyuria, determined by a midstream clean-catch (MSCC) or catheterized (indwelling or straight catheter) urine specimen with greater than or equal to 10 white blood cells (WBCs) per high-power field (hpf) on standard examination of urine sediment or greater than or equal to 10 WBCs/mm³ in unspun urine.
4. One positive urine culture within 48 hours of enrollment.

Exclusion Criteria:

1. Complete obstruction of any portion of the urinary tract (requiring a permanent indwelling urinary catheter or instrumentation), a known ileal loop, or intractable vesico-uretral reflux.
2. A temporary indwelling urinary catheter is in place and cannot be removed at study entry.
3. Perinephric or intrarenal abscess or known or suspected prostatitis.
4. Uncomplicated UTI.
5. Any history of recent accidental trauma to the pelvis or urinary tract.

6. Any amount of effective antibiotic therapy after obtaining the urine culture for admission to this study and prior to the administration of the first dose of IV study therapy.
7. An infection which has been treated with greater than 24 hours of systemic antibiotic therapy known to be effective against the presumed or documented etiologic pathogen(s) within the 72-hour period immediately prior to consideration for entry into the study.
8. History of serious allergy, hypersensitivity (e.g., anaphylaxis), or any serious reaction to carbapenem antibiotics, any cephalosporins, penicillins, or other β -lactam agents.
9. History of serious allergy, hypersensitivity (e.g., anaphylaxis), or any serious reaction to other beta-lactam inhibitors (e.g., tazobactam, sulbactam, clavulanic acid).
10. History of a seizure disorder.
11. Currently being treated with valproic acid or has received treatment with valproic acid in the 2 weeks prior to screening.
12. Rapidly progressive or terminal illness unlikely to survive the approximately 6 to 8 week study period.
13. Pregnant or expecting to conceive, breast feeding, or plans to breast feed within 1 month of completion of the study.
14. A response to all study therapy (IV study therapy or subsequent oral ciprofloxacin) within the timeframe of treatment specified in this protocol is considered unlikely.
15. Concurrent infection that would interfere with evaluation of response to the study antibiotics.
16. Need for concomitant systemic antimicrobial agents in addition to those designated in the various study treatment groups.
17. cUTI due to a confirmed fungal pathogen.
18. Currently receiving immunosuppressive therapy, including use of high-dose corticosteroids.
19. Prior recipient of a renal transplantation.
20. Laboratory abnormalities as specified in protocol.
21. History of any other illness that, in the opinion of the investigator, might confound the results of the study or pose additional risk in administering the study drug.
22. Currently participating in, or has participated in, any other clinical study involving the administration of investigational or experimental medication (not licensed by regulatory agencies) at the time of presentation or during the previous 30 days prior to screening or is anticipated to participate in such a clinical study during the course of this trial.
23. Estimated or actual creatinine clearance of <50 mL/minute.