Multi-center, Randomized, Open-label Trial to Evaluate the Efficacy of Oral Fosfomycin versus Oral Levofloxacin Strategies in Complicated Urinary Tract Infections (FOCUS)

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Version Number*:* 4.0

Day Month Year
10 July 2019

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with Good Clinical Practice (GCP) and as required by:

United States (US) 45 Code of Federal Regulations (CFR) Part 46 (Protection of Human Subjects).

Food and Drug Administration (FDA) Regulations 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (Institutional Review Boards), 21 CFR Part 11 and21 CFR Part 312 (Investigational New Drug Application).

International Conference on Harmonisation (ICH) E6: GCP; 62 Federal Register 25691 (1997); and future revisions.

Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

National Institutes of Health (NIH) Office of Extramural Research, Research Involving Human Subjects, as applicable.

National Institute of Allergy and Infectious Diseases (NIAID) Clinical Terms of Award, as applicable.

Applicable Federal, State, and Local Regulations and Guidance.

SIGNATURE PAGE

The signature below provides the necessary assurance that the trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH E6: GCP guidelines.

I agree to conduct the trial in compliance with GCP and applicable regulatory requirements.

I agree to conduct the trial in accordance with the current protocol and will not make changes to the protocol without obtaining approval from the sponsor and institutional review board (IRB)/institutional ethics committee (IEC), except when necessary to protect the safety, rights, or welfare of subjects.

Site Investigator Signature:

Signed: _____ Date: _____

Name

Title

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
AESI	Adverse Event of Special Significance
ARLG	Antibiotic Resistance Leadership Group
AUC	Area Under the Curve
BUN	Blood Urea Nitrogen
CDAD	*Clostridioides difficile*-associated diarrhea
CFR	Code of Federal Regulations
CFU	Colony Forming Units
CIOMS	Council for International Organizations of Medical Sciences
CLSI	Clinical & Laboratory Standards Institute
CMS	Clinical Materials Services
COI	Conflict of Interest
CONSORT	Consolidated Standards of Reporting Trials
Cr	Creatinine
CrCl	Creatinine Clearance
CRE	Carbapenem-resistant Enterobacteriaceae
CRF	Case Report Form
CRO	Contract Research Organization
CROMS	Clinical Research Operations and Management Support
cUTI	Complicated Urinary Tract Infection
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DSMB	Data and Safety Monitoring Board

ECG	Electrocardiogram
E. coli	*Escherichia coli*
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	Electroencephalogram
EOT	End of Therapy
ESBL	Extended-spectrum beta-lactamase
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FOCUS	Fosfomycin Oral in Complicated Urinary Tract Infections
FWA	Federalwide Assurance
GCP	Good Clinical Practice
GI	Gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council of Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IDES	Internet Data Entry System
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISV	Interim Study Visit
IV	Intravenous
JAMA	Journal of the American Medical Association

LAR	Legally Authorized Representative
MDR	Multi-drug Resistant
MedDRA®	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
Micro-ITT	Microbiological Intent-to-Treat population
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NCI	National Cancer Institute, NIH, DHHS
NDA	New Drug Application
NEJM	New England Journal of Medicine
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OCRA	Office of Clinical Research Affairs, DMID, NIAID, NIH, DHHS
OER	Office of Extramural Research
OHRP	Office for Research Protections
OHSR	Office for Human Subjects Research
ORA	Office of Regulatory Affairs, DMID, NIAID, NIH, DHHS
PAD	Pharmacokinetics And Dynamics for FOCUS
PHI	Protected Health Information
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SMA	Secondary Medical Assessor
SDCC	Statistical Data and Coordinating Center
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOCS	Safety Oversight Committee Support
SOP	Standard Operating Procedure
TMP-SMX	Trimethoprim-Sulfamethoxazole
TOC	Test of Cure
US	United States
USA	United States of America
UTI	Urinary Tract Infection
uUTI	Uncomplicated Urinary Tract Infection
VRE	Vancomycin-resistant Enterococci
VTEU	Vaccine and Treatment Evaluation Unit
WBC	White Blood Cell
WHO	World Health Organization

PROTOCOL SUMMARY

Title:	Multi-center, Randomized, Open-label Trial to Evaluate the Efficacy of Oral Fosfomycin versus Oral Levofloxacin Strategies in Complicated Urinary Tract Infections (FOCUS).
Phase:	4
Population:	Approximately 634 subjects with complicated urinary tract infections (cUTIs) without bacteremia with a uropathogen; male and female, aged ≥18 years, in the US.
Sites/Facilities Enrolling Participants:	Up to 15 US sites.
Study Duration:	25 months.
Subject Participation Duration:	28 days.
Description of Agent or Intervention:	**Strategy 1**: Initial OR step-down therapy with fosfomycin 3 grams, oral powder, once daily and if indicated a subsequent investigator-directed adjustment to another adequate oral therapy. **Strategy 2**: Initial OR step-down therapy with levofloxacin 750 mg, oral tablet, once daily and if indicated a subsequent investigator-directed adjustment to another adequate oral therapy. Initial therapy is defined as the first effective agent and step down therapy is defined as with prior effective agents. The dosing of oral therapy depends on creatinine clearance (CrCl). Refer to schematic of study design (Figure 1) on indications for investigator-directed adjustment and definition of another adequate oral therapy.

Objectives:

The objective of the trial is to compare the safety and efficacy of two pragmatic strategies (Strategy 1 vs Strategy 2) as initial or step-down therapies for cUTI, including pyelonephritis.

Primary:

- To compare Strategy 1 and Strategy 2 in terms of treatment success rates at TOC.

Secondary:

- To assess the safety of fosfomycin.
- To compare Strategy 1 and Strategy 2 in terms of solicited adverse events.
- To compare Strategy 1 and Strategy 2 in terms of treatment success rates at EOT.

Exploratory:

- To compare Strategy 1 and Strategy 2 in terms of treatment success rates at EOT, separately analyzing subjects with pyelonephritis vs. other types of cUTI.
- To compare Strategy 1 and Strategy 2 in terms of treatment success rates at TOC, separately analyzing subjects with pyelonephritis vs. other types of cUTI.
- To compare Strategy 1 and Strategy 2 in terms of clinical cure rates at EOT.
- To compare Strategy 1 and Strategy 2 in terms of clinical cure rates at TOC.
- To compare Strategy 1 and Strategy 2 in terms of microbiological success rates at EOT.
- To compare Strategy 1 and Strategy 2 in terms of microbiological success rates at TOC.
- To compare Strategy 1 and Strategy 2 in terms of adjustment-free treatment success rates at EOT.
- To compare Strategy 1 and Strategy 2 in terms of adjustment-free treatment success rates at TOC.

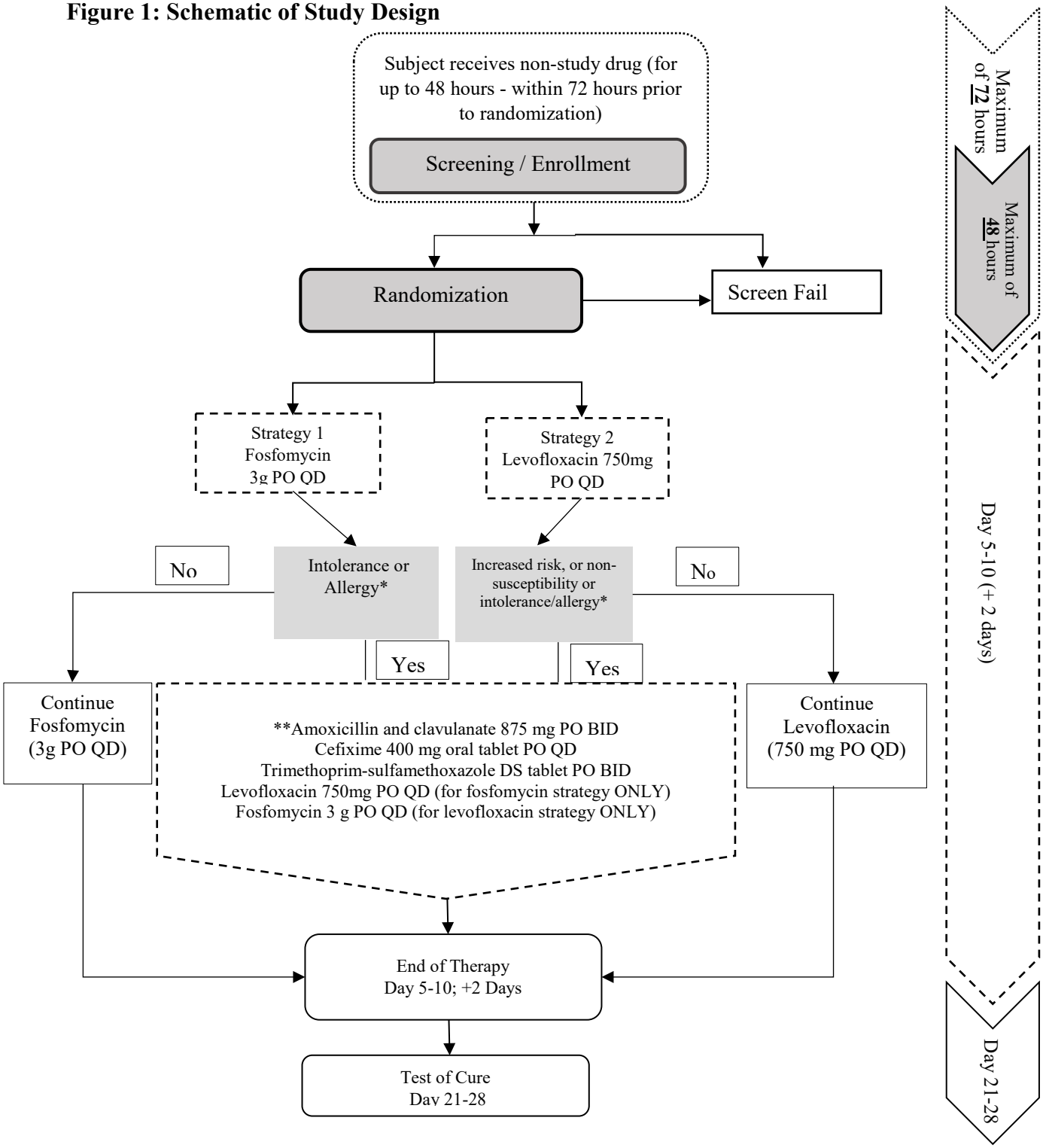
- To compare Strategy 1 and Strategy 2 in terms of number of days of antibiotic at TOC.
- To compare Strategy 1 and Strategy 2 in terms of relapse infection rates after EOT.
- To compare Strategy 1 and Strategy 2 for subjects with in vitro non susceptibility to fosfomycin in terms of treatment success rates at EOT.
- To compare Strategy 1 and Strategy 2 for subjects with in- vitro non susceptibility to levofloxacin in terms of treatment success rates at EOT.
- To compare rates of discontinuation in subjects treated with Strategy 1 vs. Strategy 2 due to occurrence of a significant related adverse event.
- To compare Strategy 1 and Strategy 2 for subjects with in vitro heteroresistance to fosfomycin or levofloxacin in terms of treatment success rates at EOT.
- To compare Strategy 1 and Strategy 2 for subjects with in vitro heteroresistance to fosfomycin or levofloxacin in terms of treatment success rates at TOC.

Description of Study Design:

This is a phase 4, multi-center, open-label, randomized pragmatic superiority clinical trial comparing two strategies for initial or step-down oral therapy of cUTI without bacteremia with a uropathogen after 0-48 hours of parenteral antibiotic therapy.

Estimated Time to Complete Enrollment: Approximately 24 months.

Figure 1: Schematic of Study Design



*Investigator-directed adjustment is indicated one time in the trial if the pathogen shows in-vitro non susceptibility to the initial or step-down levofloxacin therapy, ***OR*** if the subject develops an intolerance or allergy to the initial or step-down therapy and at the investigator's discretion, ***OR*** the subject has an underlying condition posing increased risk for adverse events from quinolone therapy.

Another adequate oral therapy is defined as an oral therapy to which the pathogen shows in-vitro susceptibility ***AND* to which the subject is tolerant based on history ***AND*** which is listed below:

- Levofloxacin 750 mg oral tablet once daily (Strategy 1 only)
- Fosfomycin 3 grams oral powder once daily (Strategy 2 only)
- Amoxicillin-clavulanate 875/125 mg oral tablet twice daily
- Cefixime 400 mg oral tablet once daily
- Trimethoprim-sulfamethoxazole (TMP-SMX 160/800 mg) double-strength oral tablet twice daily

The duration of oral study therapy (initial + investigator-directed adjustment if indicated) in each strategy is 5-7 days of any of the above antibiotics to which the pathogen is susceptible.

The dosing of oral therapy depends on creatinine clearance (CrCl) (Section 6.2).

Modifications of study drug dose are done during the interim study visit (ISV).

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2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1. Background Information

In the US, cUTIs are a widespread clinical problem in both community and healthcare-associated settings, and a major cause of urgent care center, emergency department, and hospital admissions associated with significant morbidity and mortality, as well as a high economic burden (Edwards et al., 2009; Al Hasan et al., 2011).

cUTIs include ascending UTIs that rise above the level of the bladder (e.g., pyelonephritis), and UTIs that occur in patients with anatomic or functional abnormalities of the urinary tract, with significant medical or surgical co-morbidities (e.g., diabetes, pregnancy, renal failure, urinary tract obstruction, presence of an indwelling urethral catheter, ureteral stent, nephrostomy tube, or urinary diversion, renal transplantation, or immunosuppression), or are hospitalized. cUTIs are caused by a greater variety of organisms with an increased likelihood of antimicrobial resistance as compared to uncomplicated UTIs (Mazzuli, 2012).

Escherichia coli (*E. coli*) cause ~60-80% of community-acquired UTIs and ~50% of hospital-acquired UTIs. Other Gram-negative organisms that frequently cause UTIs are *Klebsiella* spp., *Proteus* spp., *Enterobacter* spp., *Serratia marcescens*, and *Pseudomonas aeruginosa*. Gram-positive organisms such as *Enterococcus* spp., coagulase-negative staphylococci, and *Staphylococcus aureus* are also commonly implicated (Koeijers et al., 2010). Less virulent organisms do not commonly cause disease in the setting of uncomplicated UTIs, but can cause severe and invasive disease in the setting of cUTIs (Mazzuli, 2012).

The treatment of cUTIs has become increasingly complex due to rising antibiotic resistance, particularly among Gram-negative bacteria. Community strains of Enterobacteriaceae, including *E. coli*, now show fluoroquinolone-resistance rates that reach or exceed 10-30% in many parts of the US. In some parts of the world, such strains show fluoroquinolone-resistance rates that exceed 40%. Approximately half of fluoroquinolone-resistant strains also express extended-spectrum beta-lactamases (ESBLs), making them resistant to all beta-lactam antibiotics except carbapenems. Such strains are typically also resistant to TMP-SMX, eliminating most available oral antibiotics for cUTI. In the absence of effective oral therapy for cUTI, patients may require prolonged parenteral therapy with carbapenems. Thus, there is a critical need for alternative oral therapy strategies to treat cUTIs.

2.2. Rationale

Levofloxacin at 750 mg daily is FDA-approved for the treatment of cUTI and the current standard of care in the US. Levofloxacin is a concentration-dependent antibacterial; therefore, the ratio of area under the curve (AUC) or peak level to minimum inhibitory concentration

(MIC) are the main parameters predicting bacterial eradication (Klausner et al., 2007). Because the AUC/MIC or peak/MIC ratios determine the likelihood of bacterial eradication, the use of the higher 750-mg dose of levofloxacin may more effectively eradicate pathogens and prevent amplification of resistant clones (Jumber et al., 2003) or clones with intermediate resistance. However, resistance to these first-line antimicrobial agents has become increasingly common in all uropathogens leading to treatment failure and additional empiric or step-down therapies are needed for cUTI (Qiao, 2013).

In the US, a tromethamine salt of fosfomycin has been FDA-approved since 1996 as a single oral sachet for the treatment of uncomplicated UTIs (e.g., cystitis). Fosfomycin has broad in-vitro antibacterial activity against many clinically significant multidrug resistant uropathogens and excellent penetration into the urinary tract. In a recent surveillance study of 658 UTI clinical isolates collected in 2012 in the U.S., MIC_{90} values of fosfomycin were 64 mg/L for E. coli, 32 mg/L for Klebsiella spp., 32 mg/L for Proteus spp., and 32 mg/L for Enterobacter spp. This translates to 99.6% susceptibility for E. coli when applying the FDA and CLSI susceptibility breakpoint of 64 mg/L (Keepers, 2017).The increase in antimicrobial resistance has driven the off-label use of frequent dosing of fosfomycin for cUTI. In a retrospective study in which only half of patients were clinically evaluable, the majority achieved clinical success (96%) and microbiological cure (75%) (Giancola, 2017) for complicated or multidrug-resistant UTIs. In observational studies, AEs following oral or parenteral administration have been generally mild, and parenteral doses up to 24 grams/day and for many weeks for subacute diseases (e.g., osteomyelitis) have been safely administered (Corti, 2003). However, a recent controlled phase 1 trial evaluating the pharmacokinetics, pharmacodynamics, safety, and tolerability of two dosing regimens of oral fosfomycin in healthy adult subjects in the US (PROOF, NCT02570074) showed high incidence of AEs with the majority (57%) being related to grade 1 diarrhea. More than 75% of subjects reported some type of gastrointesintal AE. No subjects discontinued the study due to an AE. Two subjects had grade 3 AEs [transaminitis and *Clostridioides difficile*-associated diarrhea (CDAD)], both of which resolved without sequelae (Bleasdale, 2017).

The goal of this trial is to evaluate the safety and efficacy of two different strategies as initial or step-down oral therapy of cUTI without bacteremia with a uropathogen, including pyelonephritis: a strategy of initial or step-down oral fosfomycin, administered at a dose of 3 grams once daily with one investigator-directed adjustment if needed for tolerability (Strategy 1), vs. a strategy of initial or step-down oral levofloxacin, administered at a dose of 750 mg once daily with one investigator-directed adjustment if needed for tolerability or non susceptible clinical isolate (Strategy 2).

Investigator-directed adjustment if needed in oral antibiotic choice is permitted once in this pragmatic design as in-vitro susceptibility and tolerability data, such as non susceptibility to levofloxacin or intolerance or allergy to the initial or step-down therapy leading to fosfomycin or levofloxacin discontinuation, become available (Figure 1). The dosing of oral therapy depends

on creatinine clearance (CrCl) (Section 6.2). The total duration of study drug administration is 5-7 days of any per protocol antibiotic to which the pathogen is susceptible.

2.3. Potential Risks and Benefits

Fluoroquinolones exert broad-spectrum antimicrobial activity against most UTI pathogens, achieve high levels in the urinary tract, and are comparable or superior to other broad-spectrum antibiotics, including parenteral regimens, making them ideal agents to treat cUTIs. However, given that fluoroquinolone has concerning side effects and increased resistance among community and hospital-acquired uropathogens, and that no new oral antibiotics for treatment of UTIs are expected to become available for several years, there is a critical need for an alternative strategy for the treatment of cUTI. The alternative to oral fluoroquinolones for cUTIs will increasingly be prolonged parenteral therapy for these infections, with attendant side effects from intravenous (IV) catheterization and healthcare contact. Thus, there are potentially societal and patient benefits to studying different pragmatic strategies as initial or step-down therapies for cUTIs including fosfomycin along with other drugs approved for cUTI. This flexible design strategy avoiding prolonged use of parenteral antibiotics for treatment of cUTI, mitigates the risk of in-vitro resistance to quinolones, and potentially resolves significant AEs from either initial or step-down therapy to levofloxacin or fosfomycin.

2.3.1. Potential Risks

Fosfomycin

For ~40 years, tens of thousands of patients in Europe have been treated with fosfomycin for a variety of infections. This drug has been well-tolerated, with a side effect profile like other frequently used antibiotics (detailed below), and long-term toxicities have not been described with a single dose.

Clinical trials experience: The following drug-related AEs were reported in >1% of individuals:

Table 1: Drug-Related Adverse Events (%) for Fosfomycin and Comparator Antibiotics

Adverse Events	Fosfomycin (N=1233)	Nitrofurantoin (N=374)	TMP-SMX (N=428)	Ciprofloxacin (N=455)
Diarrhea	9.0	6.4	2.3	3.1
Vaginitis	5.5	5.3	4.7	6.3
Nausea	4.1	7.2	8.6	3.4
Headache	3.9	5.9	5.4	3.4
Dizziness	1.3	1.9	2.3	2.2
Asthenia	1.1	0.3	0.5	0.0
Dyspepsia	1.1	2.1	0.7	1.1

Source: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ad155d62-9b49-4a50-a2ae-d3aad8155936

The following AEs, regardless of drug relationship, were observed in ≥1% (up to 10%) of individuals: diarrhea, headache, vaginitis, nausea, rhinitis, back pain, dysmenorrhea, pharyngitis, dizziness, abdominal pain, dyspepsia, asthenia, and rash.

The following AEs, regardless of drug relationship, were observed in <1% of individuals: abnormal stools, anorexia, constipation, dry mouth, dysuria, ear disorder, fever, flatulence, flu syndrome, hematuria, infection, insomnia, lymphadenopathy, menstrual disorder, migraine, myalgia, nervousness, paresthesia, pruritus, increased serum glutamic pyruvic transaminase (SGPT), skin disorder, somnolence, and vomiting. One patient developed unilateral optic neuritis, considered possibly related to fosfomycin.

Post-marketing experience: The following SAEs were rare in fosfomycin-treated individuals outside the US: angioedema, anaphylaxis, aplastic anemia, asthma exacerbation, cholestatic jaundice, hepatic necrosis, toxic megacolon, and hearing loss.

Laboratory changes: The following laboratory changes, regardless of drug relationship, were reported in US clinical trials of fosfomycin: increased eosinophil count, increased or decreased white blood cell (WBC) count, increased bilirubin, increased SGPT and serum glutamic oxaloacetic transaminase (SGOT), increased alkaline phosphatase, decreased hematocrit, decreased hemoglobin, increased and decreased platelet count. These changes were generally transient and were not clinically significant.

Overdosage: In acute toxicology studies, oral administration of high fosfomycin doses (up to 5 grams/kg) were well-tolerated in mice and rats, produced transient and minor instances of watery stool in rabbits, and produced diarrhea with anorexia in dogs occurring 2-3 days after a single dose. These doses represent 50-125 times the human therapeutic dose. The following AEs were observed in patients taking fosfomycin in overdose: vestibular loss, impaired hearing, metallic taste, and general decline in taste perception. In the event of overdosage, treatment is symptomatic and supportive.

Levofloxacin

Levofloxacin has been licensed in the US since 1996 and is currently used as first-line therapy for cUTI. However, the FDA recently warned that "serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections who have other treatment options." These include tendinopathy and tendon rupture, aortic dissection or rupture exacerbation of myasthenia gravis, hypersensitivity reactions, hepatotoxicity, central nervous system effects (with convulsions, toxic psychoses, increased intracranial pressure), peripheral neuropathy, CDAD, prolongation of the QT interval, dysglycemia, photosensitivity or phototoxicity, and development of drug-resistant bacteria.

Clinical trials experience: The following drug-related AEs were reported in >1% of individuals:

Table 2: Drug-Related Adverse Events (%) for Levofloxacin

System/Organ Class	Adverse Event	% (N=7537)
Infections and Infestations	Moniliasis	1
Psychiatric Disorders	Insomnia	4
Nervous System Disorders	Headache	6
	Dizziness	3
Respiratory, Thoracic, and Mediastinal Disorders	Dyspnea	1
Gastrointestinal Disorders	Nausea	7
	Diarrhea	5
	Constipation	3
	Abdominal pain	2
	Vomiting	2
	Dyspepsia	2
Skin and Subcutaneous Tissue Disorders	Rash	2
	Pruritus	1
Reproductive System and Breast Disorders	Vaginitis	1 (N=3758 women)
General Disorders and Administration Site Conditions	Edema	1
	Injection site reaction	1
	Chest pain	1

Source: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8962eb50-3366-1eec-44f9-170e686d2d66

The following AEs, regardless of drug relationship, were observed in <1% of individuals: genital moniliasis, anemia, thrombocytopenia, granulocytopenia, allergic reaction, hypo/hyperglycemia, hyperkalemia, anxiety, tremor, agitation, confusion, depression, hallucination, nightmare, sleep disorder, anorexia, abnormal dreaming, convulsions, paresthesia, vertigo, hypertonia, hyperkinesias, abnormal gait, somnolence, syncope, epistaxis, cardiac arrest, palpitation, ventricular tachycardia/arrhythmia, phlebitis, gastritis, stomatitis, pancreatitis, esophagitis, gastroenteritis, glossitis, pseudomembranous/*Clostridioides difficile* colitis, abnormal hepatic function, increased hepatic enzymes, increased alkaline phosphatase, urticaria, myalgia, skeletal pain, arthralgia, tendinitis, abnormal renal function, and acute renal failure.

Post-marketing experience: Although causality has not been established, during post-marketing surveillance, the following events have occurred in patients prescribed levofloxacin: pancytopenia, aplastic anemia, leukopenia, hemolytic anemia, eosinophilia, anaphylactic or

anaphylactoid reactions, anaphylactic shock, angioneurotic edema, serum sickness, psychosis, paranoia, suicide attempt and suicidal ideation, myasthenia gravis exacerbation, anosmia, parosmia, ageusia, dysgeusia, peripheral neuropathy (may be irreversible); encephalopathy, abnormal electroencephalogram, dysphonia, pseudotumor cerebri, uveitis, vision disturbance, including diplopia, visual acuity reduced, vision blurred, scotoma, hypoacusis, tinnitus isolated reports of torsade de pointes, electrocardiogram (ECG) QT prolongation, tachycardia, vasodilatation, allergic pneumonitis, hepatic failure (including fatal cases), hepatitis, jaundice, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, photosensitivity or phototoxicity reaction, leukocytoclastic vasculitis, tendon rupture, muscle injury (including rupture), elevated muscle enzymes, rhabdomyolysis, interstitial nephritis, multi-organ failure, pyrexia, prolonged prothrombin time, and elevated international normalized ratio.

Cefixime

Cefixime is licensed in the US for treatment of uncomplicated UTIs and other indications.

Cefixime is contraindicated for anyone with a known allergy to cephalosporins. SAEs possibly associated with this drug include hypersensitivity reactions, CDAD, coagulopathies, and development of drug-resistant bacteria.

Clinical trials experience: The most common AEs were GI upset (up to 30%), diarrhea (16%), loose or frequent stools (6%), abdominal pain (3%), nausea (7%), dyspepsia (3%), and flatulence (4%). About 5% of patients discontinued therapy because of drug-related AEs.

Post-marketing experience: The following AEs were reported in <2% of patients taking cefixime: pseudomembranous colitis, transient hepatic and/or renal failure, neurologic symptoms (headaches, dizziness, seizures), genital pruritus, vaginitis, candidiasis, transient thrombocytopenia, leukopenia, neutropenia, prolongation in prothrombin time, elevated LDH, pancytopenia, agranulocytosis, eosinophilia, hyperbilirubinemia, allergic reactions, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, and colitis.

Source: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=5007152e-a679-4e85-ac3f-c46087812774

Amoxicillin-clavulanate

Amoxicillin-clavulanate is licensed in the US for treatment of UTIs and other indications. It is contraindicated in any patient with a history of allergic reaction to penicillin or hepatic dysfunction. Serious and potentially fatal anaphylactic reactions are more common with penicillin allergies. Other SAEs include hepatoxicity and CDAD.

Clinical trials experience: The most common AEs were diarrhea or loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%), and vaginitis (1%). About 3% of patients discontinued therapy because of drug-related AEs. The overall incidence of AEs, especially diarrhea, increased with the higher recommended dose. Less common AEs (<1%) were abdominal discomfort, flatulence, and headache.

Post-marketing experience: Many AEs/SAEs have been reported during post-marketing use mostly affecting the following organ systems: gastrointestinal, skin, liver, renal, hematologic and lymphatic, central nervous system.

Source: *https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d567412a-e5ed-4c7f-90f0-ea3039786480*

Trimethoprim-sulfamethoxazole

TMP-SMX is licensed in the US for treatment of UTIs and other indications.

TMP-SMX is contraindicated in anyone with a known allergy to TMP or sulfonamides, a history of drug-induced thrombocytopenia, megaloblastic anemia due to folate deficiency, or hepatic and/or renal deficiency.

Adverse reactions: The most common AEs are GI disturbances (nausea, vomiting, anorexia) and allergic skin reactions (rash, urticaria). The following SAEs are rare, but can be fatal:

- Hematologic: Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia.
- Allergic reactions: Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills, Henoch-Schonlein purpura, serum sickness-like syndrome, generalized allergic reactions, generalized skin eruptions, photosensitivity, conjunctival and scleral injection, pruritus, urticaria, rash, periarteritis nodosa, and systemic lupus erythematosus.
- Gastrointestinal: Hepatitis (including cholestatic jaundice and hepatic necrosis), elevation of serum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, and anorexia.
- Genitourinary: Renal failure, interstitial nephritis, elevated BUN and serum Cr levels, toxic nephrosis with oliguria and anuria, crystalluria and nephrotoxicity in association with cyclosporine.
- Metabolic and nutritional: Hyperkalemia and hyponatremia.
- Neurologic: Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, and headache.

- Psychiatric: Hallucinations, depression, apathy, and nervousness.
- Endocrine: The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides), and oral hypoglycemic agents. Cross-sensitivity may exist with these agents. Diuresis and hypoglycemia rarely occur in patients receiving sulfonamides.
- Musculoskeletal: Arthralgia and myalgia. Isolated cases of rhabdomyolysis have been reported, mainly in AIDS patients.
- Respiratory: Cough, shortness of breath, and pulmonary infiltrates.
- Miscellaneous: Weakness, fatigue, and insomnia.

Post-marketing experience: Since gaining FDA approval, the following AEs have also been reported (Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure): thrombotic thrombocytopenia purpura, idiopathic thrombocytopenic purpura, and QT prolongation resulting in ventricular tachycardia and torsade de pointes.

Source: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1ba409b6-8dcd-41d2-aa9e-81b77f87ea14

2.3.2. Known Potential Benefits

The potential benefit is the possible demonstration that for patients with cUTI caused frequently by a multidrug-resistant pathogen, initial or step-down strategies to orally administered antibiotics can avoid prolonged hospital stays and the need for parenteral antibiotics.

3. OBJECTIVES AND OUTCOME MEASURES

3.1. Study Objectives

The objective of this trial is to compare the safety and efficacy of two pragmatic strategies (Strategy 1 vs Strategy 2) as initial or step-down therapies for cUTI without bacteremia with a uropathogen, including pyelonephritis.

Definitions:

Clinical cure is defined as:

- Resolution of UTI symptoms from presentation (fever, hypothermia, chills or rigors or warmth, flank pain, flank tenderness, suprapubic pain, pelvic pain, suprapubic tenderness, nausea, vomiting, pain on urination, urinary frequency, urinary urgency)

AND

- No new UTI symptoms

AND

- Avoidance of parenteral antibiotic therapy, in or out of hospital, at any time after randomization ***OR*** oral antibiotic therapy different from per protocol

Microbiological success is defined as:

- Reduction of the pathogen found at presentation to $<10^4$ CFU/mL for non-catheter specimens or $< 10^3$ for catheter specimens on urine culture.

Treatment success is defined as:

- Clinical cure and microbiological success.

Adjustment-free treatment success is defined as:

- Treatment success without therapy adjustments.

Relapse infection is defined as:

- Recurrence of UTI symptoms between EOT and TOC.

3.1.1. Primary

- To compare Strategy 1 and Strategy 2 in terms of treatment success rates at TOC.

3.1.2. Secondary

- To assess the safety of fosfomycin.
- To compare Strategy 1 and Strategy 2 in terms of solicited adverse events.
- To compare Strategy 1 and Strategy 2 in terms of treatment success rates at EOT.

3.1.3. Exploratory

- To compare Strategy 1 and Strategy 2 in terms of treatment success rates at EOT, separately analyzing subjects with pyelonephritis vs. other types of cUTI.
- To compare Strategy 1 and Strategy 2 in terms of treatment success rates at TOC, separately analyzing subjects with pyelonephritis vs. other types of cUTI.
- To compare Strategy 1 and Strategy 2 in terms of clinical cure rates at EOT.
- To compare Strategy 1 and Strategy 2 in terms of clinical cure rates at TOC.
- To compare Strategy 1 and Strategy 2 in terms of microbiological success rates at EOT.
- To compare Strategy 1 and Strategy 2 in terms of microbiological success rates at TOC.
- To compare Strategy 1 and Strategy 2 in terms of adjustment-free treatment success rates at EOT.
- To compare Strategy 1 and Strategy 2 in terms of adjustment-free treatment success rates at TOC.
- To compare Strategy 1 and Strategy 2 in terms of number of days of antibiotic at TOC.
- To compare Strategy 1 and Strategy 2 in terms of relapse infection rates after EOT.
- To compare Strategy 1 and Strategy 2 for subjects with in vitro non susceptibility to fosfomycin in terms of treatment success rates at EOT.

- To compare Strategy 1 and Strategy 2 for subjects with in vitro non susceptibility to levofloxacin in terms of treatment success rates at EOT.

- To compare rates of discontinuation in subjects treated with Strategy 1 vs. Strategy 2 due to occurrence of a significant related adverse event.

- To compare Strategy 1 and Strategy 2 for subjects with in vitro heteroresistance to fosfomycin or levofloxacin in terms of treatment success rates at EOT.

- To compare Strategy 1 and Strategy 2 for subjects with in vitro heteroresistance to fosfomycin or levofloxacin in terms of treatment success rates at TOC.

3.2. Study Outcome Measures

3.2.1. Primary

- The difference in the proportion of subjects achieving treatment success at TOC between Strategy 1 and Strategy 2.

3.2.2. Secondary

- The number of solicited and unsolicited AEs grade 2 and above in subjects receiving fosfomycin for the duration of fosfomycin use until 2 days after last dose.

- The number of serious adverse events (SAEs) in subjects receiving at least two doses of fosfomycin during the trial.

- The difference in rates and severity of solicited AEs in subjects in Strategy 1 and Strategy 2.

- The difference in the proportion of subjects achieving treatment success at EOT between Strategy 1 and Strategy 2.

3.2.3. Exploratory

- The difference in the proportion of subjects achieving treatment success at EOT between Strategy 1 and Strategy 2, stratified by pyelonephritis vs. other types of cUTI.

- The difference in the proportion of subjects achieving treatment success at TOC between Strategy 1 and Strategy 2, stratified by pyelonephritis vs. other types of cUTI.

- The difference in the proportion of subjects achieving clinical cure at EOT between Strategy 1 and Strategy 2.

- The difference in the proportion of subjects achieving clinical cure at TOC between Strategy 1 and Strategy 2.

- The difference in the proportion of subjects achieving microbiological success at EOT between Strategy 1 and Strategy 2

- The difference in the proportion of subjects achieving microbiological success at TOC between Strategy 1 and Strategy 2.

- The difference in the proportion of subjects achieving treatment success at EOT with an adjustment-free strategy between Strategy 1 and Strategy 2.

- The difference in the proportion of subjects achieving treatment success at TOC with an adjustment-free strategy between Strategy 1 and Strategy 2.

- The difference in the number of days of unique antibiotics prescribed between randomization and TOC between Strategy 1 and Strategy 2.

- The difference in the proportion of subjects having a relapse infection after EOT between Strategy 1 and Strategy 2.

- The difference in the proportion of subjects having fosfomycin in-vitro non susceptibility with treatment success at EOT between Strategy 1 and Strategy 2.

- The difference in the proportion of subjects having levofloxacin in vitro non susceptibility with treatment success at EOT between Strategy 1 and Strategy 2.

- The difference in the proportion of fosfomycin-treated subjects from both Strategy 1 and Strategy 2 between levofloxacin-susceptible and levofloxacin-non susceptible isolates.

- The difference in discontinuation rate of initial fosfomycin in Strategy 1 and initial levofloxacin in Strategy 2 because of a significant related adverse event.

- The difference in the proportion of subjects having levofloxacin heteroresistance with treatment success at EOT between Strategy 1 and Strategy 2.

- The difference in the proportion of subjects having levofloxacin heteroresistance with treatment success at TOC between Strategy 1 and Strategy 2.

- The difference in the proportion of subjects having fosfomycin heteroresistance with treatment success at EOT between Strategy 1 and Strategy 2.

- The difference in the proportion of subjects having fosfomycin heteroresistance with treatment success at TOC between Strategy 1 and Strategy 2.

4. STUDY DESIGN

This is a Phase 4, multi-center, open-label, randomized pragmatic superiority clinical trial comparing two strategies for initial or step-down oral therapy for cUTI without bacteremia with a uropathogen after 0-48 hours of parenteral antibiotic therapy. The trial will evaluate the success and safety of a strategy of initial or step-down fosfomycin, administered at a dose of 3 g once daily, vs. a strategy of initial or step-down levofloxacin administered at a dose 750 mg once daily. Initial therapy is defined as the first effective agent and step down therapy is defined as with prior effective agents. Investigator-directed adjustment to another adequate oral therapy is allowed 1) if the causative pathogen is not susceptible in vitro to quinolone initial or step-down therapy in a subject randomized to the levofloxacin strategy, ***OR*** 2) if the subject develops an intolerance or allergy to the initial or step-down oral therapy and at the investigator's discretion, ***OR*** 3) the subject has an underlying condition posing increased risk for adverse events from quinolone therapy. Another adequate oral therapy is defined as an oral therapy to which the pathogen shows in-vitro susceptibility ***AND*** to which the subject is tolerant based on history ***AND*** which is listed below:

- Levofloxacin 750 mg oral tablet once daily (Strategy 1 only)
- Fosfomycin 3 grams oral powder once daily (Strategy 2 only)
- Amoxicillin-clavulanate 875/125 mg oral tablet twice daily
- Cefixime 400 mg oral tablet once daily
- Trimethoprim-sulfamethoxazole (TMP-SMX) 160/800 mg double-strength oral tablet twice daily

The duration of oral study therapy (initial + investigator-directed adjustment if indicated) in each strategy is 5-7 days of any per protocol antibiotic to which the pathogen is susceptible such that the total duration of effective antibacterial therapy (including pre-study administration of oral therapy escalated to parenteral therapy or parenteral therapy alone) is 7 days. The dosing of oral therapy depends on creatinine clearance (CrCl) (Section 6.2).

The trial will enroll approximately 634 patients with cUTI from outpatient and inpatient settings over ~24 months. Each subject will be followed for safety and efficacy up to 28 days according to the Schedule of Study Procedures and Evaluations (Appendix A). Safety oversight will follow DMID guidelines (Section 9), and be provided by a Data and Safety Monitoring Board (DSMB)

Subjects/subject's legally authorized representative (LAR) providing informed consent and meeting all subject's study eligibility criteria will be enrolled in the trial. Subjects must have an appropriate pretreatment urine specimen obtained and submitted to the local laboratory for quantitative culture. Any isolated bacterial pathogens (Appendix B) will be identified by genus and species and will be quantified at the local laboratory. The causative agent of cUTI is

typically identified at a density of $\geq 10^5$ CFU/mL on urine culture. However, for this study, a positive culture is defined as below:

Table 3: Microbiological Intent to Treat Population

	Catheter Sample	Non-Catheter Sample
Positive Urine Culture	≥10,000	≥50,000
Microbiologic Cure	<1,000	<10,000
Contamination Allowed	None	Yes only if contaminant density ≤40,000

All pathogen(s) cultured at the local laboratory will be sent to a designated central laboratory for confirmation of fosfomycin susceptibility testing results, and for biobanking of bacterial isolates. Fosfomycin susceptibility data for a given subject to be available generally within 2-3 months. All of the susceptibility data will be returned to each site as they are generated.

Enrolled subjects must complete a Randomization Visit within 72 hours without receiving more than 48 hours of parenteral antimicrobial therapy (please refer to exclusion criteria #3) . Enrolled subjects may continue to receive parenteral standard-of-care therapy per their primary medical team until they are ready for oral step-down therapy. Subjects who are enrolled but have more than 48 hours elapse before randomization will be withdrawn from the trial and referred to primary medical provider. Within 48 hours of enrollment, when subjects are ready to switch to an oral step-down therapy, they will be randomized (1:1) to Strategy 1 or Strategy 2 and receive their first dose of study drug. Subjects can also be randomized without receiving prior non-study parenteral antibiotics.

In some instances, where an adjustment to the list of oral antibiotics is not possible if the subject experiences a clinical/microbiologic failure ***OR*** if the subject develops bacteremia with a uropathogen after randomization, the subject will be considered treatment failure and referred to the primary medical provider for further management (most commonly parenteral therapy).

5. STUDY ENROLLMENT AND WITHDRAWAL

The trial will be conducted in male and non-pregnant female subjects aged ≥18 years who are diagnosed with cUTI without bacteremia with a uropathogen. The trial is a multi-site study enrolling approximately 634 subjects (randomized 1:1).

Subjects will be recruited from inpatient and outpatient settings (clinics, urgent care clinics, emergency departments, hospital wards). Once identified, the subject/subject's LAR and the subject's primary medical team will be approached for study participation before any screening procedures or tests are carried out. The trial will be discussed with the subject/subject's LAR through the informed consent process and any questions will be answered.

Subject Inclusion/Exclusion Criteria must be confirmed by a study clinician licensed to make medical diagnoses.

No exemptions are granted on Subject Inclusion/Exclusion Criteria in DMID-sponsored studies. Questions about eligibility will be directed to the DMID Medical Officer.

5.1. Subject Inclusion Criteria

Subjects may be included in the trial if they meet ALL of the following criteria:

1. Have documented clinical signs and/or symptoms of cUTI at diagnosis[1].

[1]*Clinical signs and symptoms of cUTI include either:*

a. *Pyelonephritis, as indicated by at least 2 of the following:*

- *Documented fever (temperature >38°C) accompanied by symptoms of rigors, chills, or "warmth"*
- *Flank pain*
- *Costovertebral angle tenderness on physical exam*
- *Nausea or vomiting*
- *Dysuria, urinary frequency, or urinary urgency*

OR

b. *Complicated lower UTI, as indicated by:*

- *At least 2 of the following new or worsening symptoms of cUTI:*
  - *Dysuria, urinary frequency, or urinary urgency*
  - *Documented fever (temperature >38°C) accompanied by symptoms of rigors, chills, or "warmth"*
  - *Documented hypothermia (temperature <35.5°C)*
  - *Suprapubic pain or pelvic pain*
  - *Suprapubic tenderness on physical exam*

- *New onset of foul smell to urine or increased cloudiness of urine per subject or their caregiver*
- *Nausea or vomiting*

AND

- *At least 1 of the following complicating factors:*
  - *Males with documented history of urinary retention*
  - *Indwelling urinary catheter that is planned to be removed or replaced during study therapy and before EOT*
  - *Current obstructive uropathy that is scheduled to be medically or surgically relieved during study therapy and before EOT*
  - *Any functional or anatomical abnormality of the urogenital tract (including anatomic malformations or neurogenic bladder) with voiding disturbance resulting in at least 100 mL of residual urine OR with the need for intermittent or ongoing self-catheterization.*

2. Able to understand and provide written informed consent[2].

   [2]*A legally acceptable representative may provide consent if the subject is unable to do so, provided this is approved by local institution-specific guidelines.*

3. Anticipated to be able to be stepped down or initially started on study oral antibiotic therapy within 48 hours of enrollment[3, 4].

   [3] *The readiness of a subject for initial or step-down oral therapy is determined by the primary medical team. In addition, for step down therapy the following conditions have to be met: temperature at randomization must be less than 38C without any rigors/chills AND the subject must have an improvement in baseline symptoms of cUTI and no new cUTI symptoms.*

   [4] *Subject may be enrolled if he/she received a non-study oral antibiotic only if it is followed by parenteral antibiotics for less than 48 hours prior to de-escalation with study drugs.*

4. Male or non-pregnant female.
5. Aged 18 years or older.
6. Women of childbearing potential[5] must agree to use an effective method of contraception[6] for the duration of the trial.

   [5] *Female is considered of childbearing potential unless postmenopausal, or surgically/non surgically sterilized and at least 3 months has passed since sterilization procedure. A woman is considered postmenopausal if her last menstrual period was ≥12 months.*

   [6] *Includes, but is not limited to, non-male sexual relationships, abstinence from sexual intercourse with a male partner, monogamous relationship with vasectomized partner who has been vasectomized for ≥180 days before the subject receiving the first dose of study drug, barrier methods such as condoms or diaphragms, effective intrauterine devices, NuvaRing®, and licensed hormonal methods such as implants, injectables but not oral contraceptives.*

7. If female of childbearing potential[5], a negative urine or serum pregnancy test within 48 hours of randomization.
8. Have pyuria (WBC count ≥10/μL in unspun urine or ≥10 per high power field in spun urine) or dipstick analysis positive (excluding "trace") for leukocyte esterase.
9. Have a pretreatment baseline urine culture specimen obtained within 48 hours before the first dose of any antibiotic is administered (including pre-study antibiotics)[7].

[7]*Subjects may be enrolled in the trial and start study drug before the investigator knows the results of the baseline urine culture.*

10. Able to reliably take, tolerate, and absorb oral medications, at the investigator's discretion.
11. Ability to understand study procedures and willing and able to comply with all required procedures and visits for the duration of the trial.

5.2. Subject Exclusion Criteria

Subjects must be excluded from the trial if they meet ANY of the following criterion:

1. Have a documented history of any moderate or severe hypersensitivity or allergic reaction to all five oral therapy options.
2. Have a concomitant infection at the time of randomization, which requires non-study systemic antibacterial therapy effective against cUTI in addition to study drug.
3. Have received more than 48 hours of a potentially therapeutic antibiotic for treatment of the current cUTI within 72 hours before randomization[8].

[8]*Except if the following apply:*

a. The subject has a known baseline urinary pathogen (urine culture positive) and has failed prior therapy clinically (persistence of inclusion criteria)

AND

b. The pathogen is known to be non-susceptible to the previous therapeutic regimen used or the urine culture remains positive with a density of ≥50,000 *CFU/mL or ≥10,000 for catheterized patients.*

4. Women breastfeeding or donating breast milk.
5. Have intractable UTI infection at baseline that the investigator anticipates would require >7 days of study drug therapy.
6. Have complete, permanent obstruction of the urinary tract[9].

[9]*Patients with complete permanent obstruction expected to be medically or surgically treated prior to EOT are eligible.*

7. Have confirmed fungal UTI at time of randomization (with $\geq 10^3$ fungal CFU/mL).
8. Have suspected or confirmed perinephric or intrarenal abscess.
9. Have suspected or confirmed prostatitis, epididymitis.
10. Have an ileal loop or known vesico-ureteral reflux.
11. Have a current urinary catheter that is not scheduled to be replaced before EOT[10].

[10]*Intermittent straight catheterization or replacement of new nephrostomy catheters is acceptable.*

12. Have planned inpatient urological intervention(s) for suspected infected kidney stone or any other planned urological procedure with anticipated antibiotic prophylaxis between randomization and EOT.

13. Have bacteremia with a uropathogen causing cUTI.
14. Have an estimated or calculated CrCl ≤20 mL/min or currently receiving hemo- or peritoneal dialysis at screening.
15. Have any condition or circumstance that, in the opinion of the investigator, would compromise the safety of the subject or the quality of study data[11].

    [11] *Including any rapidly progressing disease or immediately life-threatening (acute hepatic failure, respiratory failure or septic shock).*
16. Have participated in any interventional trial of an investigational product within 30 days before the proposed first day of study drug administration.
17. Plans to participate or currently enrolled in any interventional study of an investigational agent for the duration of the trial.
18. Previous randomization in this trial.
19. Any recent (<4 weeks) history of trauma to the pelvis or urinary tract.
20. Prior fosfomycin use in the past 12 months.

5.3. Treatment Assignment Procedures

5.3.1. Randomization Procedures

Per ICH E6: GCP, screening records will be kept at each site to document the reason why an individual was screened, but failed trial entry criteria. The reasons why individuals failed screening will be recorded in the Data Coordinating Center's (DCC's) AdvantageEDC^{SM} (Electronic Data Capture) system.

Once consented and upon entry of demographic data and confirmation of eligibility for the trial, the subject will be enrolled. Enrollment of subjects will be done online using the enrollment module of AdvantageEDC^{SM}. Subjects will be randomized 1:1 to receive oral therapy from Strategy 1 vs. Strategy 2. Subjects will be stratified by (1) pyelonephritis vs. other cUTIs and (2) participating site.

The list of randomized treatment assignments will be prepared by statisticians at the DCC (The Emmes Corporation) and included in the enrollment module of its Internet Data Entry System (IDES). IDES will assign each subject a treatment code and treatment assignment from the list after demographic and eligibility data have been entered.

Instructions for use of the enrollment module are included in the AdvantageEDC^{SM} User's Guide. Manual back-up procedures and instructions are provided for use in case the site temporarily loses access to the Internet or the online enrollment system is unavailable.

5.3.2. Masking Procedures

None; this is an open-label trial.

5.3.3. Reasons for Withdrawal and Discontinuation of Study Product Administration

Subject withdrawal

Subjects/subject's LAR may voluntarily withdraw their consent for study participation at any time without penalty or loss of benefits to which they are otherwise entitled.

Subjects diagnosed with bacteremia with a uropathogen after randomization are considered study failures, and will only be followed for safety and referred to standard of care for treatment.

The investigator may also discontinue a subject for other reasons; however, follow-up safety evaluations will be conducted if the subject/subject's LAR agrees. If a subject withdraws from or is discontinued before completion of the trial, the reason will be recorded in the electronic case report form (eCRF).

Additional reasons for withdrawal might include, but are not limited to, the following:

- Medical disease or condition, or new clinical finding(s) for which continued participation, in the opinion of the investigator or the patient's primary medical provider, might compromise the safety of the subject.
- Subject is lost to follow-up.
- Termination of the trial.

Having a uroptahogen(s) density below the defined cut-offs does not, alone, constitute a reason for withdrawal of the subject from the study.

Study Drug Discontinuation

Subjects who discontinue study drug should remain in study and be assessed for safety and clinical/microbiological success per defined criteria (Section 3.1). Discontinuation of study drug does not, per se, cause withdrawal from the trial nor by itself constitute treatment failure.

5.3.4. Handling of Withdrawals and Discontinuation of Administration

An early termination occurs when an enrolled subject ceases participation in the trial, regardless of circumstances, before the final TOC visit. The reason(s) for early termination should be reflected in the source documentation and applicable eCRF. If a subject ceases participation in the trial, the subject will be encouraged to be followed for safety and any ongoing AEs at the time of withdrawal will be followed to resolution.

The investigator will inform the subject that data already collected will be retained and analyzed even if the subject withdraws from the trial.

In all cases, the reasons why a subject is withdrawn will be recorded in detail and entered in the eCRF. As much as possible, all EOT procedures will be performed on all subjects who do not complete the trial per protocol.

If the subject fails treatment, he/she will be referred to the primary medical provider for further management.

5.3.5. Subject Replacement

Subjects/subject's LAR who sign the ICF and are randomized but do not receive study drug (e.g decline assignment to a specific strategy), or are randomized and treated, but subsequently withdraw; or are withdrawn or terminated from the trial; or are lost to follow-up will not be replaced. If the study drop-out rate exceeds 20%, the Principal Investigator (PI) will, in consultation with the ARLG and the sponsor, determine if replacement rules and/or study design need to be revised.

5.3.6. Termination of Study

If the trial is prematurely terminated by the sponsor, any regulatory authority, or the investigator for any reason, the investigator will promptly inform the subjects, assure appropriate therapy or follow-up for the subjects, as necessary, and provide a detailed written explanation of the termination to the IRB/IEC.

6. STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1. Study Product Description

Fosfomycin: a synthetic, broad-spectrum, bactericidal antibiotic for oral administration. It is available as a single-dose sachet which contains white granules consisting of 5.631 grams of fosfomycin tromethamine (equivalent to 3 grams of fosfomycin), and the following inactive ingredients: mandarin flavor, orange flavor, saccharin, and sucrose.

Levofloxacin: a synthetic broad-spectrum antibacterial agent. Levofloxacin is a light yellowish-white to yellow-white crystal or crystalline powder with an empirical formula of $C_{18}H_{20}FN_3O_4$ ● ½ H20 and the molecular weight is 370.38. The 750 mg film-coated tablet (expressed in the anhydrous form) contains the following inactive ingredients: hypromellose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, and polysorbate 80.

6.1.1. Acquisition

Fosfomycin and levofloxacin will be obtained from the DMID Clinical Materials Services (CMS); (Fisher BioServices), upon request by the study sites and approval by DMID.

Amoxicillin-clavulanate, cefixime, and TMP-SMX are options of adequate oral therapies for investigator-directed adjustment and will be acquired locally at each site.

6.1.2. Formulation, Packaging, and Labeling

Fosfomycin: is supplied as a single-dose sachet containing the equivalent of 3 grams of fosfomycin. The investigational study product Fosfomycin will be labeled according to manufacturer specifications and include the statement “Caution: New Drug-Limited by Federal (or United States) law to investigational use.”

Levofloxacin: is supplied as a 750 mg capsule-shaped, film-coated tablet for oral administration.

Additional Oral Therapy:

Cefixime: is supplied as a 200 mg chewable tablet, 400 mg capsule, or tablet, or oral suspension (100 mg/ 5mL and 200 mg/5 mL) for oral administration.

Amoxicillin-clavulanate: is supplied as a tablet in the following strength: 875mg/125mg. The 875mg/125mg film-coated tablet is a white-off-white capsule shaped tablet. Each tablet contains 875 mg amoxicillin anhydrous and 125 mg clavulanate acid for oral administration.

TMP-SMX: is supplied as a tablet in the following strength: 160 mg/800 mg (double strength). The 160 mg/800 mg double strength (DS) tablet for oral administration contains 800 mg SMX and 160 mg TMP.

The additional oral therapies (Cefixime, Amoxicillin-clavulanate, and TMP/SMX) will be prepared and labeled in accordance to the clinical site's pharmacy standard operating procedures (SOPs)

6.1.3. Product Storage and Stability

Fosfomycin tromethamine powder must be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Levofloxacin tablets must be stored at 20°C to 25°C (68° to 77°F) in well-closed containers.

Cefixime, Amoxicillin-clavulanate, and TMP-SMX Store per manufacturer's instructions.

6.1.4. Dosage, Preparation and Administration of Study Intervention/Investigational Product

Fosfomycin is administered orally as one 3-gram single-dose sachet into 3-4 ounces (1/2 cup) of cool water; each dose must be taken immediately after dissolving in water. Hot water should not be used to dissolve fosfomycin. It may be taken either with or without food for normal kidney function. If CrCl is ≤20 mL/min, fosfomycin should be taken as 3 grams every other day.

Levofloxacin 750 mg is administered orally as one tablet once daily with or without food for normal kidney function. If CrCl is 20-49 mL/min, 750 mg should be taken every other day. If on subsequent testing post-randomization the CrCl <20 mL/min, the dose is 500 mg every other day.

Cefixime 400 mg is administered orally as one tablet or capsule once daily with or without food for normal kidney function. If CrCl is between 21 to 59 mL/min, 260 mg of oral suspension should be taken once daily. If on subsequent testing post-randomization CrCl is ≤20 mL/min, 200 mg chewable tablet should be taken once daily.

Amoxicillin-clavulanate 875/125 mg is administered orally as one tablet twice daily ideally at the start of a meal for normal kidney function. If on subsequent testing post-randomization CrCl is between 10 and ≤ 20 mL/min, 500/125 mg should be taken twice daily or if CrCl is <10 mL/min, 500/125 mg should be taken once daily.

TMP-SMX 160/800 mg is administered orally as one double-strength tablet twice daily with or without food for normal kidney function. If on subsequent testing post-randomization CrCl is

between 15 and <20 mL/min, one single-strength tablet (TMP-SMX 80/400 mg) should be taken twice daily. Do not give if CrCl is <15 mL/min.

Pills will be maintained as dispensed and not scored and cut, crushed, or otherwise divided for ease of swallowing (except for Cefixime 400 mg tablet that is scored and cut if needed to dispense 200 mg for renal adjustment).

Duration of oral therapy is a total of 5-7 days of any per protocol antibiotic to which the pathogen is susceptible for a total of 7 days of effective antibacterial therapy.

CrCl will be calculated using the Cockcroft-Gault equation (Cockcroft et al., 1976) based on Cr level obtained at screening or repeat level at the investigator discretion.

For subjects who receive pre-study therapy, study drug may be initiated on the same calendar day as the last dose of pre-study therapy, consistent with the intention to orally step subjects down from parenteral non-study therapy to oral study drugs or for investigator-directed oral adjustment. Thus, on the first day of study therapy, the subject may receive both pre-study therapy and study drug. This will also apply to investigator-directed adjustments, if needed.

6.2. Modification of Study Drugs for a Subject

Adjustment of study drugs per Figure 1 as needed.

In some instances, where an adjustment to the list of oral antibiotics is not possible either for drug non-susceptibility /intolerance ***OR*** if the subject experiences a clinical/microbiologic failure ***OR*** if the subject is found to have a bacteremia with a uropathogen after randomization, the subject will be considered treatment failure and referred to the primary medical provider for further management (most commonly parenteral therapy). Subjects will continue to be followed for safety.

6.3. Accountability Procedures for the Study Drugs

The FDA requires accounting for the disposition of all investigational products. The Investigator is responsible for ensuring that a current record of product disposition is maintained, and product is dispensed only at an official study site by authorized personnel as required by applicable regulations and guidelines. Records of product disposition, as required by federal law, consist of the date received, date administered, quantity administered, and the subject number to whom the drug was administered.

The Investigational Pharmacist will be responsible for maintaining accurate records of the shipment and dispensing of the investigational product and study product sourced locally (Cefixime, Amoxicillin-clavulanate, and TMP-SMX). The pharmacy records must be available

for inspection by the DMID monitoring contractors, and are subject to inspection by a regulatory agency (e.g., FDA) at any time. An assigned study Monitor will review the pharmacy records.

Unused investigational study product (fosfomycin and levofloxacin) will be stored at 15-30ºC for fosfomycin and 20°C to 25°C for levofloxacin and all other antibiotics (cefixime, TMP-SMX, and Amoxicillin-Clavulanate) will be stored per manufacturer's storage instructions in the Investigational Pharmacy until clinical trial accountability is completed. At study termination, all unused investigational product will be disposed in accordance with the MOP following complete drug accountability and monitoring. All unused antibiotics (Cefixime, TMP-SMX, and Amoxicillin-Clavulanate) obtained locally at each site will be disposed of in accordance with the site's local SOPs.

6.4. Assessment of Subject Compliance with Study Drug

Subjects will be directly observed at the time of first dosing by a member of the clinical research team who is trained to administer the study drug. Administration will be documented on the source document and entered in the eCRF. A pill/sachet count will be performed.

6.5. Concomitant Medications/Treatments

Medications history (concomitant medications) will include a review of all current medications and medications taken within 30 days before signing the ICF through the TOC visit. Prescription and over-the-counter drugs will be included as well as herbals, vitamins, and supplements.

When co-administered with fosfomycin, metoclopramide lowers the serum concentration and urinary excretion of fosfomycin, with other drugs that increase GI motility producing similar effects. Subjects should be counseled regarding this potential interaction and metoclopramide dosing should be separated by at least 3 hours from fosfomycin dosing.

Levofloxacin should be administered at least 2 hours before or 2 hours after antacids containing magnesium or aluminum, as well as sucralfate, metal cations (e.g., iron), multivitamins containing zinc, or didanosine chewable/buffered tablets.

7. STUDY SCHEDULE

Subjects may be screened up to 48 hours before randomization. Subjects may not have received more than 48 hours of pre-study therapy within 72 hours before initiation of study drug. The total duration of effective oral antibiotics is 5-7 days of any per protocol antibiotic to which the pathogen is susceptible. However, the total duration of antibiotics therapy varies if the pathogen responsible for cUTI was not susceptible in vitro to the initial empiric regimen.

A calendar day of therapy is defined as the day on which any dose of antibiotic therapy is received.

7.1. Recruitment

Each study site will determine the most efficient procedures to identify potentially eligible subjects from primary care clinics, urgent care centers, emergency departments and inpatient wards affiliated with the study clinical trial centers. Medical providers will be informed about the study and provided with site-specific FOCUS provider information pamphlets summarizing the study design and participant eligibility criteria. Providers may also be asked to alert their patients about their practice's participation in the FOCUS study, instructing them that study personnel may contact them to discuss potential research opportunities. The identification of potentially eligible subjects will vary by site and practice setting and will include direct communication with providers, review of clinical intake logs, and electronic health record alerts that automatically screen for new urinary tract infection cases from medical records.

7.2. Visit 00: Screening/Enrollment (Days 1-2)

After the subject/subject's LAR has provided informed consent and the ICF has been signed and dated, the following procedures will be completed, and data will be entered in AdvantageEDC^{SM}, according to Appendix A. All procedures and tests must occur within 48 hours before initiation of study drug.

- Collection of focused medical history
- Review inclusion/exclusion criteria
- Collection of concomitant medications
- Collection of method of birth control (female subjects only)
- Optional limited physical exam (abdominal, flank, and suprapubic palpation, and examination of any other body site as indicated by subject symptomatology) with vital signs (blood pressure, heart rate, respiration rate, temperature)

- Measurement of weight and height
- Assessment of cUTI signs and symptoms at presentation
- Optional assessment of cUTI signs and symptoms at screening/baseline visit
- Pregnancy test (serum or urine) for females of childbearing potential if not already obtained as part of standard of care. Clinical laboratory tests including serum chemistries, hematology, and urinalysis at presentation if not already obtained as part of standard of care
- Collection of urine cultures if not already obtained as part of standard of care
- Review urine and blood culture results if available
- Collection of blood cultures if not already obtained as part of standard of care
- Record results of screening laboratory tests and calculate CrCl or collection of blood for these tests if not already done.

Visit 01: Randomization/Study Drug Initiation (Day 1-3)

The subject/subject's LAR will have completed the informed consent process during the screening period. The subject must be randomized within 48 hours of initiation of screening procedures and must receive study drug the same calendar day as randomization. Screening and randomization can occur on the same day. Treatment assignment will be by randomization.

The following procedures will be completed, according to Appendix A.

- Collection of interim medical history
- Review inclusion/exclusion criteria to verify continued eligibility
- Review of concomitant medications
- Collection of vital signs (blood pressure, heart rate, respiration rate, temperature)
- Limited physical exam (abdominal, flank, and suprapubic palpation, and examination of any other body site as indicated by subject symptomatology)
- Assessment of cUTI signs and symptoms.

- Ensure pregnancy test (serum or urine) for females of childbearing potential is within 48 hours before initiation of study drug
- Enroll subject in AdvantageEDC^{SM}
- Randomize subject
- Discontinue pre-study therapy. Administer first dose of study drug. Investigator-directed adjustment may be needed as detailed in Figure 1.
- The subject will be directly observed at the time of first dosing by a member of the clinical research team. Provide instructions for its subsequent dosing and storage.
- Dispense memory aid and thermometer and provide instructions for their use
- Collection of AEs grade 2 and above and AESI of any grade occurring after the first dose of study drug
- Review urine culture and blood culture results if available

7.3. Follow-up

Visit 02: Interim Study Visit (Active Study Drug Day 2-4)

There is one pre-planned ISV.A Phone call will be made to each subject enrolled in the study to follow-up on health status and review memory aid. If an antibiotic therapy is to be changed, a clinic visit in person is required to receive new antibiotic therapy.

The following will be obtained:

- Review of concomitant medications
- Assessment of study drug compliance (pill or sachet count if in person visit)
- Review of memory aid and assessment of solicited adverse events
- Assessment of cUTI signs and symptoms and investigator's assessment of improvement
- Limited physical exam (abdominal, flank, and suprapubic palpation, and examination of any other body site as indicated by subject symptomatology) with vital signs, if indicated when symptoms are present and if the visit is done in person
- Collection of AEs and SAEs grade 2 and above, and AESI of any grade.

- Review of urine and blood culture results (if not available at screening/randomization)
- Investigator-directed adjustment per Figure 1 if needed.

If an adjustment is needed, the duration of all initial or step-down therapy is 5-7 days of any per protocol antibiotic to which the pathogen is susceptible. For example, subjects experiencing a significant related AE from fosfomycin/levofloxacin on Day 3 will need 2-4 days of investigator-directed adjustment oral therapy. However, subjects on levofloxacin at Day 3 (Strategy 2) who are found to have a cUTI pathogen with in-vitro non-susceptibility to quinolone will need 7 days of investigator-directed adjustment of effective oral therapy.

Visit 03: End of Therapy Visit (Day 5-10 + 2)

The EOT visit will occur within 2 days of the completion of oral therapy. At the EOT visit, subjects will be assessed for clinical and microbiological outcome and safety. If the subject experiences a clinical/microbiologic failure, the subject will be referred to the primary medical provider for further management. An EOT visit will occur even for subjects who stopped study drug before EOT.

The following procedures will be completed according to Appendix A.

- Review of concomitant medications
- Assessment of study drug compliance (pill/sachet count)
- Review of memory aid and assessment of solicited adverse events
- Assessment of cUTI signs and symptoms and investigator's assessment of improvement
- Limited physical exam (abdominal, flank, and suprapubic palpation, and examination of any other body site as indicated by subject symptomatology) with vital signs (blood pressure, heart rate, respiration rate, temperature)
- Collection of blood sample for blood culture if subject is febrile and/or at investigator's discretion
- Collection of urine specimen for culture
- Collection of AEs and SAEs grade 2 and above, and AESI of any grade.
- Collection of blood (t=24 hours) and urine (t=4-24 hours) if subject consented for Future Use Samples and Data (Section 7.8)

7.4. Visit 03A: Follow-up for subjects whose last dose of antibiotic per protocol is fosfomycin (Day 7-12 + 2)

If the EOT visit is completed less than two days after the last dose of fosfomycin, the subject will be contacted to follow-up on safety. This will be completed by phone.

The following will be obtained:

- Review of concomitant medications
- Review of memory aid and assessment of solicited adverse events
- Collection of AEs and SAEs grade 2 and above, and AESI of any grade

7.5. Final Study Visit

Visit 04: Test of Cure Visit (Day 21 + 7)

A TOC visit should be scheduled for 21 days (+7 days) after randomization. If the subject experiences a clinical/microbiologic failure, the subject will be referred to the primary medical provider for further management. The following procedures will be completed according to Appendix A for clinical outcome and any AEs:

- Review of concomitant medications
- Assessment of cUTI signs and symptoms and investigator's assessment of improvement
- Limited physical exam (abdominal, flank, and suprapubic palpation, and examination of any other body site as indicated by subject symptomatology) with vital signs (blood pressure, heart rate, respiration rate, temperature)
- Collection of blood sample for blood culture if subject is febrile and/or at investigator's discretion
- Collection of urine specimen for culture
- Collection of AESIs/SAEs

7.6. Early Termination Visit (if needed)

If a subject/subject's LAR withdraws (but still consents for the visit) or is withdrawn from the trial, every effort should be made to complete an early termination visit. If the subject presents to the Early Termination visit with symptoms concerning for active illness in need of medical attention, the study team will refer the subject to seek care and to follow up with their primary care provider. At the early termination visit, all assessments that would have been completed at the EOT visit should be made, including:

- Review of concomitant medications
- Assessment of study drug compliance if visit occurs before the EOT visit and collection of dispensed antibiotics.
- Review of memory aid and assessment of solicited adverse events if visit occurs before the EOT visit
- Assessment of cUTI signs and symptoms and investigator's assessment of improvement
- Limited physical exam (abdominal, flank, and suprapubic palpation, and examination of any other body site as indicated by subject symptomatology) with vital signs (blood pressure, heart rate, respiration rate, temperature)
- Collection of blood sample for blood culture if subject is febrile and/or at investigator's discretion
- Collection of urine specimen for culture
- Collection of AEs grade 2 and above or AESI of any grade if visit occurs before EOT, or SAEs if visit occurs before TOC

7.7. Unscheduled Visit (if needed)

An unscheduled study visit may be initiated by the subject/subject's LAR or investigator, if a subject is not improving on therapy, has a grade 2 and above AE/SAE/AESI, or for any other reason. In addition, the reason for the visit will be documented, including who initiated the visit, what complaints the subject/subject's LAR has, and/or what concerns the primary medical team or site investigator have. Clinical outcome and any safety assessments will be documented.

All assessments that should be completed at a scheduled visit will be completed including:

- Review of concomitant medications

- Assessment of study drug compliance if visit occurs before EOT visit
- Review of memory aid and assessment of solicited adverse events if visit occurs before EOT visit
- Assessment of cUTI signs and symptoms and investigator's assessment of improvement
- Limited physical exam (abdominal, flank, and suprapubic palpation, and examination of any other body site as indicated by subject symptomatology) with vital signs (blood pressure, heart rate, respiration rate, temperature)
- Collection of blood sample for blood culture if subject is febrile and/or at investigator's discretion
- Collection of urine specimen for culture as needed in the setting of clinical failure
- Collection of AEs grade 2 and above and AESI of any grade if visit occurs before EOT, or SAEs if visit occurs before TOC

7.8. Visit 02A: Visit for future use samples and data (if applicable)

Subjects who only received fosfomycin as part of Strategy 1 without any adjustment will be asked to have one additional optional visit and be willing to come back 24 hours later for EOT visit. The subject will be asked to bring the day's dose in and take it after the pre-dose sample is drawn. The visit will be done at Day 5-7 with the following procedures being performed

- Review of concomitant medications
- Assessment of study drug compliance
- Collection of AE grade 2 and above and AESI of any grade
- Measurement of weight
- Insertion of a peripheral intravenous catheter that will be removed by the end of the visit or performance of serial venipunctures per the participant's preference.
- Venous blood sample collection at collection at 0 (pre-dose) 0.5, 1, 2, 4 and 24 hours after the dose. The 24 hour collection will be done as part of EOT visit. Three mL of blood will be collected at each of these timepoints.
- Total voided urine collection between 0-4 hours and 4-24 hours post dose. The subject is asked to empty his/her bladder before taking the fosfomycin dose. The collection of the 4-24 hours urine will be done as part of EOT visit.

8. STUDY PROCEDURES/EVALUATIONS

8.1. Clinical Evaluations

A focused medical history will be obtained by review of the subject's medical records or by interview of the subject or LAR. Medical history will be obtained regarding significant medical disorders of the head, eyes, ears, nose, throat, mouth, cardiovascular system, lungs, GI tract, liver, pancreas, kidney, urologic system, nervous system, blood, lymph nodes, endocrine system, musculoskeletal system, skin, and genital/reproductive tract. A history of any allergies, cancer, immunodeficiency, psychiatric illness, substance abuse, and autoimmune disease will be solicited.

Medications history (concomitant medications) will include a review of all current medications and medications taken within 30 days before signing the ICF through the TOC visit. Prescription and over-the-counter drugs will be included as well as herbals, vitamins, and supplements. Use of a new medication should prompt evaluation for the presence of a new AE or diagnosis of a chronic medical disease or condition.

The limited physical exam will include abdominal, flank, and suprapubic palpation, and examination of any other body site as indicated by subject symptomatology.

Vital signs will include (depending on the visit) subject's height and weight, blood pressure, heart rate, respiration rate, and temperature.

Assessment of cUTI signs and symptoms will be performed. Signs and symptoms to be assessed include fever, hypothermia, chills, flank pain, flank tenderness, suprapubic tenderness, vomiting, pain on urination, urinary frequency, urinary urgency, foul smelling urine, and cloudy urine.

A review of memory aids will be performed by assessing solicited events from randomization until EOT visit (and up to 2 days later if subject's last study drug dose is fosfomycin).

8.2. Laboratory Evaluations

8.2.1. Clinical Laboratory Evaluations

A urine or serum pregnancy test will be performed by the local laboratory within 48 hours of randomization to study drug in all women of childbearing potential. Results must be negative and known before randomization and administration of study drug.

Clinical screening laboratory parameters to be evaluated include:

- Serum chemistries (3 mL), including creatinine, blood urea nitrogen (BUN), glucose, sodium, potassium, chloride, bicarbonate, calcium will be performed at the local laboratory and, if obtained as standard of care, within 48 hours of randomization.

- Hematology (4 mL), including complete blood count (with RBC count, hemoglobin, and hematocrit, total WBC count with differential counts, platelet count), will be performed at the local laboratory and, if obtained as standard of care, within 48 hours of randomization.

- Urinalysis, including dipstick analysis and microscopic evaluation to assess WBCs, nitrites, leukocyte esterase and squamous epithelial cells, will be performed at the local laboratory and, if obtained as standard of care, within 48 hours of randomization.

- Liver studies (3 mL) including SGOT, SGPT, alkaline phosphatase, total bilirubin. LDH, albumin, total protein, PT and PTT are not required for the trial, but will be recorded if they are obtained by the primary medical team as standard of care.

- Screening blood cultures (32-40 mL) may be performed at the local laboratory. If blood cultures are positive the patient will be considered a treatment failure and referred to the primary provider of treatment.

- Urine cultures will be performed at the local laboratory at screening, EOT, TOC and early termination visit. If a subject fails treatment at any point during the trial, an adequate and appropriate urine specimen should be obtained for culture. Urine cultures will be performed at the local laboratory and positive cultures will be sent to central laboratory. At the Emory VTEU site, back-up bacterial isolate samples not needed by the central laboratory will be tested for heteroresistance in local research lab.

8.2.2. Special Assays or Procedures

N/A

8.2.3. Specimen Preparation, Handling, and Shipping

8.2.3.1. Instructions for Specimen Preparation, Handling, and Storage

Specific instructions are included in the Manual of Procedures.

Bacterial Isolates

Bacterial isolates that grew from urine culture collected within 72 hours prior to randomization (prior to any antimicrobial therapy) will be stored locally.

Future Use Samples and Data

Pre and post-dose blood will be collected in a K2EDTA tube. In addition, total voided urine will be collected over 4 hours during the PK visit then over 20 hours to be collected at home until the second PK visit.

Plasma samples will be processed by being centrifuged for plasma separation, aliquoted and stored as specified in MOP Appendix C.

The volume and pH of the urine will be measured for each collection (0-4 hours and 4-24 hours). Urine will be processed and aliquoted from each collection and stored as specified in MOP Appendix C.

8.2.3.2. Specimen Shipment

Specific instructions are included in the Manual of Procedures.

Bacterial isolates and future-use specimens (urine and blood) will be shipped under controlled conditions in compliance with the UN 3373 guidelines. Bacterial isolates will be batch shipped at room temperature on agar tubes to the Central Laboratory. At the Emory VTEU, if back-up isolates are not needed by the central laboratory, they will be tested for heteroresistance in local research lab.

Future-use samples will be batch shipped on dry ice to the DMID Clinical Materials Services (CMS).

9. ASSESSMENT OF SAFETY

9.1. Specification of Safety Parameters

Safety will be assessed by the frequency and severity of AEs, AESIs, and SAEs.

Levofloxacin, Cefixime, Amoxicillin and clavulanate, and Trimethoprim-sulfamethoxazole are FDA-approved drugs for the treatment of UTI with established and well-described safety profile and NIAID does not expect that any new drug related safety signal will be detected in this trial. As such, the safety data collection will be targeted to collect Suspected Unexpected Serious Adverse Reaction (SUSAR) for all agents, grade 2 and above solicited adverse events and AESIs as specified in this protocol and grade 2 and above unsolicited adverse events and SAEs only for subjects taking 2 or more doses of fosfomycin

9.2. Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Any deaths, any related SAEs, and AESIs will be sent to the ~~SMC~~ DSMB chair for review within two business days of the DMID's Medical Monitor assessment.

9.2.1. Adverse Events

Adverse Event:

ICH E6: GCP defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to study drug. FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

AEs, including solicited adverse events, will be captured on the appropriate data collection form and eCRF. Information to be collected for (un)solicited non-serious AEs includes event description, date of onset, assessment of severity, relationship to study drug, and alternate etiology (assessed only by those with the training and authority to make a diagnosis and listed on Form FDA 1572 as an investigator), date of resolution, seriousness, and outcome. AEs occurring during the trial collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

Any medical condition that is present at the time the subject is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases, it will be recorded as an AE.

All AEs must be graded for severity and relationship to study drug (see definitions). AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop date of each reported AE will be recorded on the appropriate data collection form and eCRF.

Only Grade 2 and above AEs and SAEs will be reported.

Severity of Event:

Solicited AEs will be assessed by the investigator using a protocol-defined grading system (Table 4). For unsolicited AEs, the following guidelines will be used to quantify severity:

- Mild (Grade 1): Events require minimal or no treatment; do not interfere with the subject's daily activities.
- Moderate (Grade 2): Events result in a low level of inconvenience or concern with therapeutic measures; may cause some interference with functioning and daily activities.
- Severe (Grade 3): Events interrupt the subject's daily activities and may require systemic drug therapy or other treatment; are usually incapacitating.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the AE at each level of intensity to be performed.

Relationship to Study Drug:

The assessment of the relationship of an AE to administration of study drug is made only by those with the training and authority to make a diagnosis and listed on Form FDA 1572 as an investigator, and based on all available information at the time of eCRF completion. Whether the AE is related or not is not a factor in determining what is or is not reported in the trial. If there is any doubt whether a clinical observation is an AE, the event should be reported. Only AEs grade 2 and above are reported.

In a clinical trial, study drug must always be suspect. To help assess relatedness, the following guidelines are used:

Related – There is a reasonable possibility that study drug caused the AE, meaning that there is evidence to suggest a causal relationship between study drug and the AE.

Not Related – There is not a reasonable possibility that study drug caused the AE.

9.2.2. Solicited Adverse Events

Solicited AEs are AEs that are common following administration of these types of antibiotics. The solicited AEs will be collected after first dose of study product is given and until the EOT. If subject is on fosfomycin, solicited AEs will be collected for 2 days after last dose of fosfomycin or until EOT, whichever occurs last.

Only grade 2 and above solicited AEs will be reported.

The following Toxicity Grading Scales will be used to grade solicited AEs:

Table 4: Solicited Adverse Events Grading Scale

Solicited AE	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Insomnia	Mild difficulty falling asleep or staying asleep, or waking up early	Moderate difficulty falling asleep or staying asleep, or waking up early	Severe difficulty falling asleep or staying asleep, or waking up early
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours, or some interference with activity	Any use of narcotic pain reliever, or prevents daily activity
Dizziness	No interference with activity, or mild unsteadiness or sensation of movement	Some interference with activity, or moderate unsteadiness or sensation of movement	Prevents daily activity, or severe unsteadiness or sensation of movement
Nausea	No interference with activity	Some interference with activity	Prevents daily activity, or requires IV hydration
Vomiting	1-2 episodes in 24 hours	3-5 episodes in 24 hours	>5 episodes in 24 hours, or ER visit, or hospitalization, or requires outpatient IV hydration
Constipation	Occasional or intermittent symptoms, or occasional use of stool softeners, laxatives, dietary modification or enema	Some interference with activity, or persistent symptoms with regular use of laxatives or enemas	Prevents daily activity, or obstipation with manual evacuation indicated
Diarrhea	3 loose stools or <400 grams/24 hours	4-5 loose stools or 400-800 grams/24 hours	>5 loose stools or >800 grams/24hours, or requires IV hydration
Back pain	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours, or some interference with activity	Any use of narcotic pain reliever, or prevents daily activity
Rhinitis	No interference with activity	Some interference with activity, or local intervention required	Prevents daily activity
Pharyngitis	No interference with activity	Some interference with activity, or local intervention indicated	Prevents daily activity, or IV therapy indicated
Allergic reaction	Localized rash, or itching without rash	Diffuse rash covering multiple areas of the body	Rash requiring clinical visit
Candidiasis	Mild mucocutaneous candidiasis, requiring no treatment	Moderate mucocutaneous candidiasis, requiring topical or other over-the-counter treatment	Severe mucocutaneous candidiasis, requiring urgent

			clinical evaluation, intravenous treatment or hospitalization

9.2.3. Unsolicited Adverse Events

The unsolicited AEs will be collected only in subjects who receive at least two doses of fosfomycin from the time of second dose of fosfomycin until EOT or 2 days after last dose of fosfomycin whichever occurs last.

9.2.4. Serious Adverse Events

Serious Adverse Event (SAE):

An AE or suspected AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death,
- a life-threatening AE[1],
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or development of drug dependency or drug abuse.

[1] An AE is considered "life-threatening" if, in the view of either the site PI/designee or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE, had it occurred in a more severe form, might have caused death.

SAEs will be:

- Assessed for severity and relationship to study drug and alternate etiology,
- Recorded on the appropriate SAE data collection form and eCRF,

- Followed through resolution,
- Reviewed and evaluated by the DSMB (periodic review unless related), DMID, and IRB/IEC.

SAEs are only recorded in subjects receiving at least two doses of fosfomycin.

9.2.5. Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

Serum chemistries including Cr, BUN, glucose, sodium, potassium, chloride, bicarbonate, calcium and liver function tests (AST, ALT, alkaline phosphatase, total bilirubin) and hematology including complete blood count (with RBC count, hemoglobin, hematocrit, total WBC count with differential counts, and platelet count), will be ordered at the screening visit if not already done as standard of care.

Regular safety laboratory tests will not be ordered.

9.2.6. Adverse Events of Special Interest

AESIs are diagnoses that were retrieved by record review if a subject had an unexpected clinical encounter during the follow-up period (up to 28 days), and include the following

- *Clostridioides difficile* infection, as defined by ≥3 unformed stools (soft or watery) within 24 consecutive hours with a positive test for *Clostridioides difficile*
- Altered cardiac conduction, as defined by dysrhythmia different from subject's previously documented rhythm or a prolongation of any ECG interval by >25% from subject's previously documented ECG intervals. If no prior ECG is available for comparison, then a QTc >470 ms for men and >480 ms for women will be deemed abnormal and documented as an AESI.

Table 5: Adverse Events of Special Interest Grading Scale

AESI	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Diarrhea with a positive *C diff* test	3 loose stools or < 400 grams/24 hours	4 – 5 loose stools or 400 – 800 grams/24 hours	6 or more loose stools or > 800 grams/24 hours or requires outpatient IV hydration
Arrhythmia	Asymptomatic, intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic and incompletely controlled

			medically, or controlled with device

9.3. Reporting Procedures

9.3.1. Serious Adverse Events

SAEs will be followed until resolution even if this extends beyond the study's reporting period. Resolution of an AE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

Any AE that meets a protocol-defined serious criterion must be submitted immediately (within 24 hours of site awareness) on an SAE form to the DMID Pharmacovigilance Group:

DMID Pharmacovigilance Group

Clinical Research Operations and Management Support (CROMS)

6500 Rock Spring Dr., Suite 650

Bethesda, MD 20817, USA

SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)

SAE FAX Number: 1-800-275-7619 (US) or 1-301-897-1710 (outside US)

SAE Email Address: PVG@dmidcroms.com

In addition to the SAE form, select SAE data fields will also be entered in Advantage EDC^{SM} according to the protocol-specific MOP.

If other supporting documentation of the SAE is requested by the DMID Pharmacovigilance Group, it will be provided when the information becomes available.

The DMID Medical Monitor and DMID Clinical Project Manager will be notified of the SAE by the DMID Pharmacovigilance Group. The DMID Medical Monitor will review and assess the SAE for regulatory reporting and potential impact on subject safety and protocol conduct.

At any time after trial completion, if the site PI or designee becomes aware of an SAE that is suspected to be related to study drug, the site PI or designee will report the SAE to the DMID Pharmacovigilance Group.

9.3.2. Regulatory Reporting for Studies Conducted Under DMID-Sponsored IND

Following notification from the investigator, DMID, the Investigational New Drug (IND) sponsor, will report any suspected AE that is both serious and unexpected. DMID will report an AE as a suspected AE only if there is evidence to suggest a causal relationship between the study drug (fosfomycin) and AE. DMID will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its IND(s) or under any PI's IND(s)) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. DMID will also notify FDA of any unexpected fatal or life-threatening suspected AE as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. Follow-up information relevant to an IND safety report will be submitted as soon as the information is available. DMID will notify FDA if any halting rules are met. Upon request from FDA, DMID will submit to FDA any additional data, or information that FDA deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

All SAEs designated as "not related" to study drug will be reported to the FDA at least annually in a summary format.

9.3.3. Reporting of Pregnancy

Fosfomycin, cefixime, and amoxicillin-clavulanate are pregnancy Class B drugs; levofloxacin is a pregnancy Class C drug, and TMP-SMX is a pregnancy Class D drug. Pregnancies that occur during the study will be reported via The Emmes Corporation's IDES on the Pregnancy Report form within 5 days of site awareness.

Efforts will be made to follow all pregnancies occurring during the study through to outcome, as described in the MOP (e.g., delivery, spontaneous abortion, therapeutic abortion, etc.).

9.4. Type and Duration of Follow-up of Subjects after Adverse Events

All AEs grade 2 and above will be followed through resolution or stabilization.

Resolution of an AE/SAE/AESI is defined as the return to baseline, grade 1 or less or stabilization of the condition with the expectation that it will remain chronic.

9.5. Halting Rules

Study Halting Rules

If any of the halting rules, as outlined below, is met, further enrollment will be withheld until the DSMB reviews the safety data and provides its recommendations. The continuation of the administration of study drugs (continue the current antibiotic or switch to other one) will be at the PI discretion.

- Any death reported across the pooled study strategies, related to the treatment of fosfomycin.
- If >2 related SAEs in the same high level group term (HLGT) that are observed in subjects who take more than 1 dose of study prescribed fosfomycin, not including *Clostridioides difficile.*
- If ≥5 AESIs are observed across the pooled study strategies (≥5% if more than 100 subjects enrolled)

9.6. Safety Oversight

9.6.1. Secondary Medical Assessor

Upon DMID MM request, the principal investigator (PI) will identify a physician with relevant expertise, to act as a Secondary Medical Assessor (SMA). The SMA will examine a subject and/or medical records and provide a medical assessment (or second medical opinion) to the PI for the DMID of the safety event in question. The PI will send to the DMID MM, a summary of the event and include the PI and SMA assessments.

9.6.2. Data and Safety Monitoring Board (DSMB)

Safety oversight will be conducted by a DSMB, an independent group of experts that monitors subject safety, conducts a benefit/risk assessment, and advises DMID. DSMB members will be independent of study personnel participating in the trial, should not have scientific, financial, or other COIs related to the trial, and will have appropriate expertise to contribute to the interpretation of data from the trial.

The DSMB will conduct the following meetings:

- Organizational meeting
- Data review meeting for safety
    - Every year

- An Interim analysis for safety and efficacy after at least approximately 40% of subjects have completed the study

- Ad hoc meetings will occur when a halting rule is met, or when DMID or the DSMB chair has immediate concerns regarding observations during the trial

- Final review meeting will occur 6-8 months after the clinical database is locked to review cumulative safety and efficacy data, which will be provided in a standard summary format. The DSMB may be asked to provide recommendations in response to DMID's questions.

The DSMB will operate under the rules of a DMID-approved charter that will be written at the DSMB's organizational meeting. Procedures for DSMB reviews/meetings will be defined in the charter. Reports may include enrollment and demographic information, medical history, concomitant medications, physical assessments, clinical laboratory values, dosing compliance, and solicited and unsolicited AE/AESIs/SAEs. The DSMB will review SAEs on a regular basis and ad hoc during the trial. The DMID Medical Monitor will be responsible for reviewing SAEs in real time.

Additional data may be requested by the DSMB, and interim statistical reports may be generated as deemed necessary and appropriate by DMID. The DSMB may receive data in aggregate and presented by treatment arm. The DSMB may also be provided with expected and observed rates of the expected AEs. The DSMB will review grouped data in the closed session only. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability of proceeding with study drug administration, and to continue, modify, or terminate the trial.

10. CLINICAL MONITORING

10.1. Site Monitoring Plan

Site monitoring is conducted to ensure that the human subjects' protections, study and laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, ICH/GCP guidelines, and applicable regulations, and that the trial is conducted in accordance with the protocol, protocol-specific MOP, and applicable sponsor standard operating procedures. DMID, the sponsoring agency, or its designee will conduct site-monitoring visits as detailed in the clinical monitoring plan.

Site visits will be made at standard intervals as defined by DMID and may be made more frequently as directed by DMID. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, eCRFs, ICFs, medical and laboratory reports, and protocol and GCP compliance. Site monitors will have access to each site, study personnel, and all study documentation according to the DMID-approved site monitoring plan. Study monitors will meet with site PIs/designees to discuss any problems and actions to be taken, and will document site visit findings and discussions.

11. STATISTICAL CONSIDERATIONS

This is a phase IV multicenter, open-label, randomized pragmatic superiority clinical trial comparing two strategies for step-down oral therapy for cUTI. Participants will be followed for up to approximately 28 days.

11.1. Study Hypotheses

No particular hypothesis is made regarding the relative efficacy of the two strategies for step-down oral therapy for cUTI. However, a primary goal of the study is to compare the two strategies in terms of success (clinical cure and microbiological cure) at the test of cure visit in order to make one of three statements regarding the results of the trial: 1) Strategy 1 is superior to Strategy 2; 2) Strategy 2 is superior to Strategy 1; or 3) evidence from the trial is insufficient to conclude that either strategy is superior. Thus, the basic null hypothesis of this trial is that the probability of success at TOC is not conditional on the treatment strategy.

11.2. Sample Size Considerations

The primary analysis will be performed using the microbiological intent-to-treat (micro-ITT) population, defined as all randomized patients who have a positive baseline bacterial culture of urine (Table 3Table 4).Positive baseline culture is defined as a culture grown from a urine sample collected prior to treatment with study drug that has $\geq 10^5$ colony forming units (CFU)/mL (50,000 and above is an allowed cut-off provided it is a causative uropathogen) for non-catheter specimens **OR** $\geq 10^4$ CFU/ml for catheter specimens of a single species of bacteria that causes cUTI (Appendix B).

If a subject's baseline culture grows 2 organisms both relevant to cUTI and each in quantities ≥50,000 CFU/mL in the urine, then the baseline culture is considered positive. Cultures with 3 organisms or more grown in the urine culture will be considered contaminated unless there is a causative uropathogen that is growing at ≥50,000 CFU/ml and the contaminant are ≤40,000 CFU/ml.

For subjects with baseline cultures that grow more than one bacterial species in the urine that are not considered contaminated, microbiological success is defined as reduction of each pathogen to $<10^4$ CFU/mL on non-catheter urine culture OR $<10^3$ for catheter specimens

Patients will not be excluded from this population based upon events that occurred post-randomization (e.g., loss to follow-up). An assumption of 92% micro-ITT eligibility is made for the sample size calculations. If 634 subjects are enrolled with 1:1 allocation, 291 subjects per arm would be expected to qualify for the micro-ITT population. Assuming a 10% difference in treatment success at TOC, with 80% success for one strategy and 70% success for the other strategy, there will be 80% power to reject the null hypothesis (Section 11.1) using a two sided

ztest (without continuity correction), with a Type I error rate of 5%. These calculations assume an interim analysis after 40% of subjects have completed the study, with Type I error controlled using Lan DeMets with an O'Brien Fleming spending function. The specific success rates of 70% and 80% are based on a 10% clinically significant difference an approximate rate of success consistent with example calculations in the FDA guidance for cUTI studies. Sample size calculations were computed using PASS 2008 software. The calculations do not adjust for dropout, because analysis methods will include subjects that have dropped out early, assuming they meet micro-ITT criteria (Section 11.4).

If true success rates are instead 65% and 75%, there will be 75% power to conclude a difference in the strategies. If true success rates are 80% and 90%, there will be 92% power to conclude a difference.

11.3. Planned Interim Analyses

11.3.1. Interim Safety Review

The study will have regular reviews for safety by a DSMB, with the first review occurring approximately 12 months following the enrollment of the first participant, as described in Section 9. Assessment of study halting rules (Section 9.5) will be performed on a continual basis. There are no additional formal stopping rules based on safety data assessed in interim safety reviews.

11.3.2. Interim Safety or Efficacy Review

Only the DCC statistician and the DSMB will review interim reports of efficacy by treatment strategy. There will be one formal interim analysis of efficacy after at least approximately 40% of subjects have completed the trial. The statistical methods for the interim analysis will be fully specified in advance in a statistical analysis plan (SAP), to be prepared by the DCC. The interim analysis will be a superiority analysis of treatment success at TOC by study arm in the micro-ITT analysis population. Type I error will be controlled at a level of α=0.05 overall for the study by using Lan DeMets with an O'Brien-Fleming spending function. For the formal interim analysis of efficacy, the test of a null hypothesis of no difference in treatment success rate by treatment group will be performed as described for the primary analysis (Section 11.4). Superiority of a treatment strategy will be concluded if the null hypothesis is rejected in the formal interim analysis. The DSMB may recommend that the trial be stopped early for efficacy if one treatment strategy is concluded to be superior or for futility.

Additionally, as part of the interim analysis as well as for each regular meeting of the DSMB (closed session), 95% confidence intervals of the rate of treatment success at TOC in each treatment group using the Wilson score method will be presented using only the subset of the micro-ITT population that has treatment success versus treatment failure at TOC determined at

the time the database is locked for analysis (complete case analysis). In order to assess assumptions made regarding overall rates of treatment success (with both treatment arms combined), overall (blinded) rates of treatment success at TOC may be presented in interim reports. Also, the drop-out rate and the overall proportion of subjects eligible for micro-ITT analysis, will be presented in interim reports. If the assumption of 20% drop-out is underestimated or the assumption of 92% micro-ITT eligibility that was made for the sample size calculations overestimates eligibility for analysis, the protocol may be amended to increase the number of subjects enrolled into the study.

11.4. Final Analysis Plan

Planned analyses of all primary and secondary endpoints will be described in detail in the SAP to be prepared by the DCC and finalized prior to unblinding of the study data.

The primary analysis will be a superiority analysis of treatment success at TOC by study arm in the micro-ITT analysis population. Multiple imputation will be used in the case of missing values for treatment success at TOC in the micro-ITT population. The test of the null hypothesis of no difference between the strategies for the primary outcome (Section 11.1) will be performed using linear regression, and will include site, pyelonephritis, and number of bacterial species detected in the urine at baseline as covariates. Further details of the analysis, including the multiple imputation model, will be described thoroughly in the SAP. As a secondary analysis, a difference in treatment success at EOT by treatment strategy will be tested in the micro-ITT population, using methods analogous to the primary analysis. Sensitivity analyses will be performed for the primary analysis including a complete case analysis in which subjects are analyzed as randomized without imputation and tipping point analyses.

The safety analysis population will include all subjects receiving at least one dose of study drug. 95% confidence intervals of frequencies of solicited and unsolicited adverse events, SAEs and AESIs will be provided using the Wilson score method.

Frequency and number of solicited adverse events of grade 2 and above will be reported by treatment arm, study day, and severity, and differences between treatment arms in frequency of grade 2 and above severity solicited adverse events after the first dose of study drug will be tested using Fisher Exact Tests. For subjects receiving fosfomycin, frequency and number of each solicited adverse event of grade 2 and above severity occurring any time from date of first dose of fosfomycin in subjects receiving 2 or more doses until 2 days after last dose of fosfomycin will be tabulated.

Frequency and number of SAEs in subjects receiving at least two doses of fosfomycin during the trial will be tabulated.

For subjects receiving fosfomycin, frequency of each unsolicited adverse event of grade 2 and above severity occurring in subjects receiving at least two doses of fosfomycin until 2 days after last dose of fosfomycin will be tabulated overall and by MedDRA® System Organ Class and Preferred Term.

12. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each site will maintain appropriate medical and research records in compliance with ICH E6: Section 4.9, and regulatory and institutional requirements for the protection of confidentiality of subjects. Each site will permit authorized representatives of DMID, its designees, and appropriate regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance (QA), audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data and source documents, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at pharmacies, laboratories, and medico-technical departments involved in the trial.

13. QUALITY CONTROL AND QUALITY ASSURANCE

Following a written DMID-accepted site quality management plan, each participating site and its subcontractors are responsible for conducting routine QA and quality control (QC) activities to internally monitor study progress and protocol compliance. Each site PI will provide direct access to all source data/data collection forms, and reports for monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. Each site PI will ensure all study personnel are appropriately trained and applicable documentations are maintained at the sites.

The DCC will implement quality control procedures beginning with the data entry system and generate data QC checks that will be run on the database. Any missing or anomalous data will be communicated to the sites for clarification and resolution.

DMID-designated clinical monitors will verify that the clinical trial is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, ICH/GCP guidelines, and the applicable regulatory requirements. Clinical monitoring reports will be submitted to DMID.

14. ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1. Ethical Standard

Each site PI will ensure the trial is conducted in full conformity with principles of the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research [April 18, 1979]) and codified in 45 CFR 46, 21 CFR 50, and 21 CFR 56, as applicable. The PI will also ensure conformity with ICH E6: GCP, and applicable federal regulations, guidance, and guidelines for GCP and Clinical Trials with humans.

14.2. Institutional Review Board

Each site PI will obtain IRB/IEC approval for the protocol to be conducted at his/her research site(s), and send supporting documentation to DMID before initiating recruitment of subjects. The investigator will submit applicable information to the IRB/IEC on which it relies for the review, to conduct the review in accordance with 45 CFR 46, ICH E6: GCP, and as applicable, 21 CFR 56 (Institutional Review Boards), 21 CFR 50 (Protection of Human Subjects), and other federal, state, and local regulations. The IRB/IEC must be registered with Office for Human Research Protections (OHRP)/FDA as applicable to the research. DMID must receive the documentation that verifies IRB/IEC-approval for the protocol, associated informed consent documents, and upon request any recruitment material and handouts or surveys intended for the subjects, before the recruitment and enrollment of subjects.

Any amendments to the protocol or consent materials will be approved by the IRB/IEC before they are implemented. IRB/IEC review and approval will occur at least annually throughout the enrollment and follow-up of subjects, and may cease if annual review is no longer required by applicable regulations. The investigator will notify the IRB/IEC of deviations from the protocol and reportable SAEs, as applicable to the IRB/IEC policy.

Each institution engaged in the research will hold a current Federalwide Assurance (FWA) issued by OHRP for federally-funded research.

14.3. Informed Consent Process

Informed consent is a process that is initiated before an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Before any study procedures are performed, informed consent will be obtained and documented. Subjects/subject's LAR will receive a concise and focused presentation of key information about the trial, verbally and with a written consent form. The explanation will be organized, and presented in lay terminology and language that facilitates understanding why one might or might not want to participate.

An investigator or designee will describe the protocol to potential subjects/subject's LAR face-to-face. The key information about the purpose of the trial, the procedures and experimental aspects of the trial, risks and discomforts, any expected benefits to the subject/subject's LAR, and alternative treatments will be presented first to the subject/subject's LAR.

Subjects/subject's LAR will also receive an explanation that the trial involves research, and a detailed summary of the proposed study procedures and study interventions/products. This will include aspects of the trial that are experimental, the probability for random assignment to treatment groups, any expected benefits, all possible risks (including a statement that the particular treatment or procedure may involve risks to the subject or to the embryo or fetus, if the subject is or may become pregnant, that are currently unforeseeable), the expected duration of the subject's participation in the trial, alternative procedures that may be available and the important potential benefits and risks of these available alternative procedures.

Subjects/subject's LAR will be informed that they will be notified in a timely manner if information becomes available that may be relevant to their willingness to continue participation in the trial. Subjects/subject's LAR will receive an explanation as to whether any compensation and any medical treatments are available if injury occurs, and, if so, what they consist of, or where further information may be obtained. Subjects/subject's LAR will be informed of the anticipated financial expenses, if any, to the subject for participating in the trial, as well as any anticipated prorated payments, if any, to the subject for participating in the trial. They will be informed of whom to contact (e.g., the investigator) for answers to any questions relating to the trial.

Information will also include the foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated. The subjects/subject's LAR will be informed that participation is voluntary and that they are free to withdraw from the trial for any reason at any time without penalty or loss of benefits to which the subject is otherwise entitled.

The extent of the confidentiality of the subjects' records will be defined, and subjects/subject's LAR will be informed that applicable data protection legislation will be followed. Subjects/subject's LAR will be informed that the monitor(s), auditors(s), IRB/IEC, NIAID, and regulatory authority(ies) will be granted direct access to the subject's/subject's LAR original medical records for verification of trial procedures and/or data without violating the subject's confidentiality, to the extent permitted by applicable laws and regulations, and that, by signing a written ICF, the subject/subject's LAR is authorizing such access.

Subjects/subject's LAR will be informed that records identifying the subject will be kept confidential, and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available and, if the results of the trial are published, the subject's identity will remain confidential. Subjects/subject's LAR will be informed whether confidential information

collected from the research and/or specimens will be used for additional research, even if identifiers are removed.

Subjects/subject's LAR will be allowed sufficient time to consider participation in the trial, and to discuss the trial with their family, friends, or LAR, or think about it before agreeing to participate.

ICFs will be IRB/IEC-approved and subjects/subject's LAR will be asked to read and review the ICF. Subjects/subject's LAR must sign the ICF before starting any study procedures being done specifically for the trial.

Once signed, a copy of the ICF will be given to the subject(s)/subject(s) LAR for their records. The subject(s) /subject(s) LAR may withdraw consent at any time during the trial. The rights and welfare of the subject(s) will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in the trial.

Study personnel may employ recruitment efforts before obtaining consent with the IRB approval that chart review is allowed without a fully executed screening consent. Site clinical staff may pre-screen via chart review and refer potential subjects to the research staff. Recruitment will be from inpatient and outpatient settings (clinics, urgent care clinics, emergency departments, hospital wards). Once identified, the subject/subject's LAR and the subject's primary medical team will be approached for study participation before screening procedures or tests are carried out. Research staff would obtain written consent per the standard informed consent process before conducting protocol-specific screening activities.

New information will be communicated by the site PI to subjects/subject's LAR who consent to participate in the trial in accordance with IRB/IEC requirements. The ICF will be updated and subjects/subject's LAR will be re-consented per IRB/IEC requirements, if necessary. Subjects/subject's LAR will be given a copy of all ICFs they sign.

The sites will enroll non-English speakers (using translated ICF and other study related documents), illiterate or non-writing individuals following the requirements of local IRBs.

14.3.1. Informed Consent/Assent Process (in Case of a Minor)

N/A

14.4. Exclusion of Women, Minorities, and Children (Special Populations)

Children will be excluded from the trial as there is insufficient safety data on the use of fosfomycin in children, especially those aged <12 years. In addition, levofloxacin and several of

the alternative oral antibiotics in the protocol are not routinely prescribed as first-line therapy in children.

14.5. Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality includes documentation, investigation data, subject's clinical information, and all other information generated during participation in the trial. No information concerning the trial or the data generated from the trial will be released to any unauthorized third party without prior written approval of the DMID and the subject. Subject confidentiality will be maintained when study results are published or discussed in conferences. The study monitor, or other authorized representatives of the sponsor or governmental regulatory agencies, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in the trial. The participating sites will permit access to such records.

All records will be kept locked and all computer entry and networking programs will be carried out with coded numbers only and with password-protected systems. All non-clinical specimens, evaluation forms, reports, and other records that leave the site will be identified only by a coded number.

To protect privacy, we have received a Certificate of Confidentiality. With this Certificate, the researchers cannot be forced to release information that may identify the research subject, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify the subject, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the US Government that is used for auditing or evaluation of federally-funded projects, like this trial, or for information that must be released to meet the requirements of the FDA.

The Certificate does not prevent the subject from voluntarily releasing information about themselves or their involvement in the trial. If any person or agency obtains a written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate does not prevent the researchers from reporting without the subject's consent, information that would identify the subject as a participant in the research project regarding matters that must be legally reported including: child and elder abuse, sexual abuse, or wanting to harm themselves or others.

14.6. Study Discontinuation

If the trial is prematurely terminated by the sponsor, any regulatory authority, or the investigator for any reason, the investigator will promptly inform the subjects, assure their appropriate therapy or follow-up, as necessary, and provide a detailed written explanation of the termination to the IRB/IEC. If any subject's confidential information will continue to be collected for the trial, the IRB/IEC must approve an ICF with the study procedures, any risks and discomforts, and applicable elements, and the investigator or designee will re-consent the subjects/subject's LAR as approved by the IRB/IEC.

14.7. Costs, Subject Compensation, and Research Related Injuries

There is no cost to subjects for the research tests, procedures, and study drug while participating in the trial. Procedures and treatment for clinical care may be billed to the subject, subject's insurance, or third party. Subjects may be compensated for their participation in the trial. Compensation will be in accordance with the local IRB/IEC's policies and procedures, and subject to IRB/IEC approval.

If it is determined by the site PI that an injury occurred to a subject as a direct result of the tests or treatments that are done for the trial, then the subject will be referred to appropriate health care facilities. Study personnel will try to reduce, control, and treat any complications from the trial. Immediate medical treatment may be provided by the participating site. No financial compensation will be provided by NIAID/NIH to the subject for any injury suffered due to participation in the trial.

14.8. Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored at the SDCC. After the study is completed, the de-identified, archived data will be stored, for use possible by other researchers including those outside of the study.

With the subjects/subjects LAR approval and as approved by local IRBs, de-identified biological samples will be stored at DMID CMS with the same goal as the sharing of data with the SDCC. These samples could be used to research the causes of antimicrobial resistance, pharmacokinetic analysis, or cUTI, its complications and other conditions for which individuals with cUTI are at increased risk, and to improve treatment. The DMID CMS will be provided with a code-link that will allow linking the biological specimens with the clinical data from each participant, maintaining the blinding of the identity of the participant.

These samples may be stored temporarily at the local site or longer term at DMID CMS central clinical storage facility. They may be shared with investigators at participating sites or other institutions provided that an appropriate human subject protection plans are in place.

Residual clinical samples will be available upon completion of the trial; however, future use clinical samples may be requested from DMID and shipped from DMID CMS at any time.

The samples will not be sold or used directly for production of any commercial product. Human genetic tests will not be performed on the samples. Each sample will be labeled only with a barcode and a unique tracking number to protect subject confidentiality.

There are no benefits to subjects in the collection, storage, and subsequent use of their specimens for future research. Reports about future research done with subjects' samples will NOT be kept in their health records.

Subjects/subject's LAR may be given the option of wanting their left over samples to be used for future research or having their samples destroyed at the end of the trial. Urine samples are not optional for enrollment into the study. The subject's/subject's LAR decision can be changed at any time by withdrawing consent. If consent is withdrawn, bacterial isolates are retained if de-identified as these are not human subject's samples by notifying the study doctors or nurses in writing. However, if the subject/subject's LAR originally consents to the study and future use, and subsequently changes his/her decision, any data from a previously collected samples may still be used for the research.

15. DATA HANDLING AND RECORD KEEPING

The investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the reported data. All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue permanent ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the eCRF will be provided for use as source data collection forms and maintained for recording data for each subject enrolled in the trial. Data reported in the eCRF derived from source data collection forms will be consistent or the discrepancies will be explained.

The sponsor and/or its designee will provide guidance to the site PIs and other study personnel on making corrections to the data collection forms and eCRF.

15.1. Data Management Responsibilities

All data collection forms and laboratory reports must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. AEs must be graded, assessed for severity and causality, and reviewed by the site PI or designee. Data collection is the responsibility of the study personnel at the participating site under the supervision of the site PI. During the trial, the site PI must maintain complete and accurate documentation for the trial.

The Emmes Corporation will serve as the DCC for the trial, and will be responsible for data management, quality review, analysis, and reporting.

15.2. Data Capture Methods

Clinical data, (including, but not limited to, AEs grade 2 and above, AESI, SAEs, concomitant medications, medical history, physical assessments, and laboratory data) will be entered in a 21 CFR 11-compliant IDES provided by the DCC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

15.3. Types of Data

Data for the trial will include safety, laboratory, and outcome measures, including symptom scores and culture results.

15.4. Timing/Reports

Interim reports of safety and efficacy data on each strategy arm of the trial will be prepared for review by the DSMB at intervals defined in the DSMB charter. Interim reports for DSMB review will be structured as specified in the DSMB charter, and will be sufficiently detailed to allow the DSMB to assess study progress, feasibility, futility, quality, and safety, as appropriate. The DCC statistician will prepare and submit the interim reports in accordance with the DSMB charter.

The PI will have the responsibility of filing the DSMB review reports and providing copies to program staff. A report from DSMB review will be submitted to the local or OHRP-registered IRB/IEC, as appropriate, only if the DSMB raises any significant concerns regarding safety, confidentiality, or study integrity.

Once the study database has been locked and all primary and secondary endpoint data are available, the data will be analyzed in accordance with the Statistical Analysis Plan (Section 11.4), and a final study report will be prepared and submitted in accordance with applicable FDA/ICH guidelines.

15.5. Study Records Retention

Study documents will be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of study drug. These documents will be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

15.6. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or protocol-specific MOP requirements. The noncompliance may be either on the part of the subject, site PI, or site personnel. In response to deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3

5.1 Quality Assurance and Quality Control, Section 5.1.1

5.20 Noncompliance, Sections 5.20.1 and 5.20.2.

It is the responsibility of the site PI and personnel to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations will be promptly reported to DMID per the DCC protocol deviation reporting procedures.

All protocol deviations, as defined above, must be addressed in subject data collection forms. A completed copy of the DMID Protocol Deviation Form must be maintained in the Regulatory File, as well as in the subject's chart. Protocol deviations must be sent to the local IRB/IEC per their guidelines. The site PI and personnel are responsible for knowing and adhering to their IRB/IEC’s requirements.

16. PUBLICATION POLICY

All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central (http://www.ncbi.nlm.nih.gov/pmc/) an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH funded research. It requires investigators to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. Further, the policy stipulates that these papers must be accessible to the public on PubMed Central no later than 12 months after publication.

Refer to:

- NIH Public Access Policy, http://publicaccess.nih.gov/
- NIH Office of Extramural Research (OER) Grants and Funding, http://grants.nih.gov/grants/oer.htm

As of January 2018, all clinical trials supported by the NIH must be registered on ClinicalTrials.gov, no later than 21 days after enrollment of the first subject. Results of all clinical trials supported by the NIH, generally, need to be submitted no later than 12 months following the primary completion date. A delay of up to 2 years is available for trials that meet certain criteria and have applied for certification of delayed posting.

As part of the result posting, a copy of the protocol (and its amendments) and a copy of the Statistical Analysis Plan will be posted on ClinicalTrials.gov.

As the responsible party, DMID will register the trial and post results, and does not plan to request certification of delayed posting.

Refer to:

- Public Law 110-85, Section 801, Clinical Trial Databases
- 42 CFR Part 11
- NIH NOT-OD-16-149

17. LITERATURE REFERENCES

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18. SUPPLEMENTS/APPENDICES

APPENDIX A: SCHEDULE OF STUDY PROCEDURES AND EVALUATIONS

	Screening/ Enrollment Visit	Randomization (Study Drug Initiation) [a]	Interim Study Visit (by phone or in person)	Future Use Collection[e]	End of Therapy	Follow up[h] (phone call)	Test of Cure	Unscheduled Visit	Early Termination Visit
Visit Number	00	01	02	02 A	03	03 A	04		
Study day (window)	Day 1-2	Day 1-3		Day 7	Day 5-10 (+2 days)	Day 7-12 (+2 days)	Day 21 (+7 days)		
Study day from first dose of study drug			Day 2-4						
Informed consent	X								
Review of Inclusion/Exclusion criteria	X	X							
Medical/medication history	X	X	X	X	X	X	X	X	X
Assessment of study drug compliance			X	X	X			(X)	(X)
Dispense memory aid		X							
Review of memory aid			X		X	X		(X)	(X)
Limited physical examination [b]	(X)	X	(X)		X		X	X	X
Vital signs [b]	X	X	(X)		X		X	X	X
Weight	X			X					
Height	X								
Assessment of cUTI signs & symptoms	(X)	X	X		X		X	X	X
Investigator's assessment of improvement			X		X		X	X	X
Randomization		X							
Pregnancy test [c]	X								

Clinical Laboratory	Serum chemistries [d] (3 mL)	X								
	Hematology [d] (4 mL)	X								
	Urinalysis [d]	X								
Future use samples (optional)					X[e] 15 ml blood 10 ml urine	(X[e]) 3 ml blood 10 ml urine				
Blood cultures[f] (32-40 mL)		X				(X[f])		(X[f])	(X[f])	(X[f])
Urine specimen for culture		X[g]				X[g]		X[g]	X[g]	X[g]
Review culture results		X[i]	X[i]	X[j]						
Study drug administration			X-As Described in the Summary-X							
Collection of solicited and unsolicited[h] grade 2 and above AEs			X	X	X	X	X		(X)	(X)
Collection of AESIs			X	X	X	X	X	X	X	X
Collection of SAEs[h]			X	X	X	X	X	X	X	X

	Screening/ Enrollment Visit	Randomization (Study Drug Initiation) [a]	Interim Study Visit (by phone or in person)	Future Use Collection[e]	End of Therapy	Follow up[h] (phone call)	Test of Cure	Unscheduled Visit	Early Termination Visit
Visit Number	00	01	02	02 A	03	03 A	04		
Study day (window)	Day 1-2	Day 1-3		Day 7	Day 5-10 (+2 days)	Day 7-12 (+2 days)	Day 21 (+7 days)		
Study day from first dose of study drug			Day 2-4						
Informed consent	X								
Review of Inclusion/Exclusion criteria	X	X							
Medical/medication history	X	X	X	X	X	X	X	X	X
Assessment of study drug compliance			X	X	X			(X)	(X)
Dispense memory aid		X							
Review of memory aid			X		X	X		(X)	(X)
Limited physical examination [b]	(X)	X	(X)		X		X	X	X
Vital signs [b]	X	X	(X)		X		X	X	X
Weight	X			X					
Height	X								
Assessment of cUTI signs & symptoms	(X)	X	X		X		X	X	X
Investigator's assessment of improvement			X		X		X	X	X
Randomization		X							
Pregnancy test [c]	X								

Clinical Laboratory	Serum chemistries [d] (3 mL)	X								
	Hematology [d] (4 mL)	X								
	Urinalysis [d]	X								
Future use samples (optional)					X[e] 15 ml blood 10 ml urine	(X[e]) 3 ml blood 10 ml urine				
Blood cultures[f] (32-40 mL)		X				(X[f])		(X[f])	(X[f])	(X[f])
Urine specimen for culture		X[g]				X[g]		X[g]	X[g]	X[g]
Review culture results		X[i]	X[i]	X[j]						
Study drug administration			X-As Described in the Summary-X							
Collection of solicited and unsolicited[h] grade 2 and above AEs			X	X	X	X	X		(X)	(X)
Collection of AESIs			X	X	X	X	X	X	X	X
Collection of SAEs[h]			X	X	X	X	X	X	X	X

(X) – As indicated/appropriate.

a. Randomization and study drug initiation must occur within 48 hours of Enrollment visit.

b. Limited physical examination includes abdominal, flank, and suprapubic palpation, and examination of any other body site as indicated by subject symptomatology; vital signs include blood pressure, heart rate, respiration rate, and temperature.

c. A urine or serum pregnancy test will be performed on women of childbearing potential within 48 hours before the first dose of study drug unless performed as SOC.

d. Hematology includes complete blood count (with RBC count, hemoglobin, and hematocrit, total WBC count with differential counts, platelet count). Serum Chemistry includes Cr, BUN, glucose, sodium, potassium, chloride, bicarbonate, calcium, SGPT, SGOT, alkaline phosphatase, total bilirubin, Urinalysis includes dipstick analysis and microscopic evaluation includes for WBC, nitrites, leukocyte esterase and squamous epithelial cells. These data are gathered at baseline; if they are not obtained by the primary medical team, then the study provider should order them as study labs. LDH, albumin, total protein, PT, and PTT are not required for the study but should be recorded if ordered by the primary medical team.

e. Samples to be collected for future use on a subset of subjects who complete Strategy 1 without adjustment. The 24 hour collection of blood and urine samples will occur as part of EOT visit. Venous blood sample collection at collection at 0 (pre-dose) 0.5, 1, 2, 4 and 24 hours after the dose. The 24 hour collection will be done as part of EOT visit. Three mL of blood will be collected at each of these timepoints. Total voided urine collection between 0-4 hours and 4-24 hours post dose. The subject is asked to empty his/her bladder before taking the fosfomycin dose. The collection of the 4-24 hours urine will be done as part of EOT visit.

f. If baseline blood cultures were positive for a uropathogen after randomization, subject is considered study failure, will only be followed for safety and referred to standard of care treatment. Blood cultures are repeated if the subject is febrile and/or at the investigator's discretion.

g. An adequate and appropriate infection specimen should be obtained at the specified time points. If a subject fails treatment at any point in this study, an adequate and appropriate specimen should be obtained. The microorganisms identified from the urine culture will be sent to central study laboratory for susceptibility testing.

h. Unsolicited grade 2 and above AEs and SAEs will be recorded in subjects receiving at least 2 doses of fosfomycin. A follow up visit on Day 7-14 is done by phone and only for a subject which last dose of oral antibiotic per protocol was fosfomycin.

i. Review urine culture results if available

j. Review urine culture results if not available at screening/randomization

APPENDIX B: EXAMPLES OF CAUSATIVE PATHOGENS

The following is a list of species that may be encountered as causative pathogens in the trial. This is not intended to be an exhaustive list, as other isolates identified during the trial will be considered on a case-by-case basis. Note that yeast are not considered causative pathogens, do not define cUTI, and do not constitute eligibility for the micro-ITT population.

Gram-negative microorganisms

Acinetobacter baumannii

Acinetobacter lwoffii

Citrobacter braakii

Citrobacter freundii

Citrobacter koseri

Enterobacter aerogenes

Enterobacter cloacae

Escherichia coli

Klebsiella oxytoca

Klebsiella pneumoniae

Morganella morganii

Proteus mirabilis

Proteus vulgaris

Providencia rettgeri

Providencia stuartii

Pseudomonas aeruginosa

Serratia marcescens

Gram-positive microorganisms

Enterococcus faecalis

Enterococcus faecium

Staphylococcus aureus

Staphylococcus saprophyticus