A Phase 4, Randomized, Double-Blinded, Placebo-Controlled Trial of Azithromycin versus Doxycycline for the Treatment of Rectal Chlamydia in Men who have Sex with Men

DMID Protocol Number: 17-0092

DMID Funding Mechanism: HHSN272201300012I; HHSN27200013

Principal Investigator: [redacted]

DMID Clinical Project Manager: [redacted]

DMID Medical Monitor: [redacted]

DMID Medical Officer: [redacted]

Version Number: 4.0

22 August 2019

STATEMENT OF COMPLIANCE

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

- United States (US) 45 Code of Federal Regulations (CFR) Part 46: Protection of Human Subjects
- Food and Drug Administration (FDA) Regulations, as applicable: 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 (Electronic Records and Electronic Signatures), 21 CFR Part 312 (Investigational New Drug Application), and 21 CFR 812 (Investigational Device Exemptions)
- International Council on Harmonisation (ICH) E6 GCP guidelines; 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

All key personnel (all individuals responsible for the design and conduct of the trial) have completed Human Subjects Protection Training.

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, 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 the sponsor's approval and Institutional Review Board (IRB) / Independent Ethics Committee (IEC) approval, except when necessary to protect the safety, rights, or welfare of subjects.

Principal Investigator:

Signed: _____ Date: _____

[redacted]
University of Washington

Site Investigator:

Signed: _____ Date: _____

[redacted]
Fenway Health

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LIST OF ABBREVIATIONS

AE	Adverse Event
BID	Twice-Daily
CC	Complete Case
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence Interval
CoC	Certificate of Confidentiality
CT	*Chlamydia trachomatis*
DCF	Data Collection Form
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EMR	Electronic Medical Record
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GC	*N. gonorrhoeae*
GCP	Good Clinical Practice
GI	Gastrointestinal
HIV	Human Immunodeficiency Virus
HMC	Harborview Medical Center
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IDES	Internet Data Entry System
IDS	Investigational Drug Services
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-To-Treat
LGV	Lymphogranuloma Venereum
MOP	Manual of Procedures
MSM	Men who have Sex with Men
N	Number (typically refers to subjects)
NAAT	Nucleic Acid Amplification Test
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OTC	Over-the-Counter
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PO	Orally

PP	Per Protocol
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SDCC	Statistical and Data Coordinating Center
SIC	Screening Informed Consent
SOP	Standard Operating Procedure
STD	Sexually Transmitted Disease
STI	Sexually Transmitted Infection
US	United States
UW	University of Washington

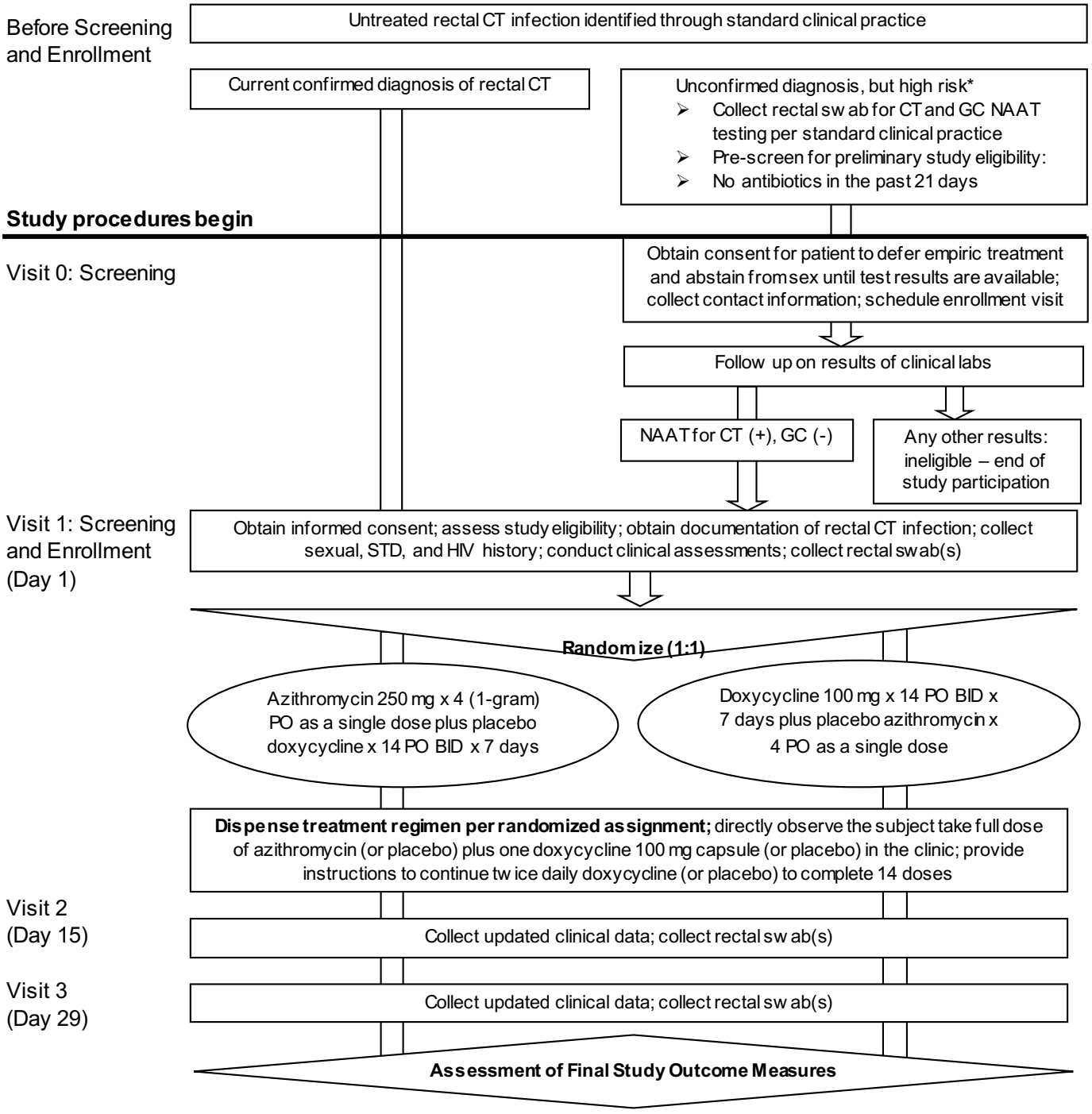
PROTOCOL SUMMARY

Title:	A Phase 4, Randomized, Double-Blinded, Placebo-Controlled Trial of Azithromycin versus Doxycycline for the Treatment of Rectal Chlamydia in Men who have Sex with Men
Phase:	4
Population:	Up to 274 adult males aged ≥18 years
Number of Sites:	Two (University of Washington, Fenway Health)
Study Duration:	Approximately 22 months
Participation Duration:	Approximately 29 days [screening/enrollment (Day 1); follow-up at Visit 2 (Day 15) and Visit 3 (Day 29)]
Description of Agent or Intervention:	Azithromycin 1 gram orally as a single dose and placebo doxycycline orally twice daily for 7 days; or placebo azithromycin orally as a single dose and doxycycline 100 mg orally twice daily for 7 days
Objectives:	Primary: • To compare the efficacy of azithromycin vs. doxycycline for treatment of rectal *Chlamydia trachomatis* (CT) infection in men who have sex with men (MSM) based on microbiologic cure [negative nucleic acid amplification test (NAAT)] at Day 29 Secondary: • To assess the effect of lymphogranuloma venereum (LGV) infection on microbiologic cure in MSM with rectal CT at Days 15 and 29 • To compare the efficacy of azithromycin vs. doxycycline for treatment of rectal CT in MSM based on microbiologic cure at Day 15 Exploratory: • To assess the effect of HIV status, adherence to study drug, antacid medication use, and symptomatic status on microbiologic cure at Day 29

Description of Study Design:	This is a Phase 4, randomized, double-blinded, placebo-controlled trial in MSM aged ≥18 years diagnosed with rectal CT. This clinical trial is designed to assess the efficacy of azithromycin 1-gram single dose or doxycycline 100 mg twice daily for 7 days with clinical follow-up visits at Days 15 and 29 for swab collection and clinical and laboratory assessments.
Estimated Time to Complete Enrollment:	21 months

Schematic of Study Design

Total N: Up to 274 subjects to achieve 246 subjects who contribute primary outcome measure data



*High risk defined as: a) known contact to chlamydia and report receptive anal intercourse in the past 30 days or b) clinician assessment that empiric treatment is indicated.

1 KEY ROLES

Individuals:	**Principal Investigator:** [redacted] University of Washington **Site Investigator:** [redacted] Fenway Health
Institutions:	
NIH – Division of Microbiology and Infectious Diseases	**DMID/NIAID/NIH** [redacted] **Medical Officer** [redacted] **Medical Monitor** [redacted] **Clinical Project Manager** [redacted]
Statistical and Data Coordinating Center	**The Emmes Corporation** [redacted]
Operations Coordinating Center	**FHI 360** [redacted]
Clinical Material Services	**University of Washington Harborview Medical Center Investigational Drug Services** [redacted]

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Chlamydia is the most frequently reported bacterial sexually transmitted infection (STI) in the US. In 2015, approximately 1.5 million cases of chlamydia were reported to Centers for Disease Control and Prevention (CDC) from 50 states and the District of Columbia, but an estimated 2.9 million infections occur annually. Rectal *Chlamydia trachomatis* (CT) infection is the most common bacterial STI among MSM in the US [1], the population at highest risk for HIV infection. Therefore, effective treatment of rectal CT is a key component of chlamydia control, and perhaps HIV prevention, for MSM. Studies in diverse healthcare settings have found that 8-12% of asymptomatic MSM test positive for rectal CT [2-5].

The 2015 CDC Sexually Transmitted Disease (STD) Treatment Guidelines for CT infection of any anatomic site recommend either a single dose of azithromycin or a 7-day course of twice-daily doxycycline. However, in practice, many clinicians treat asymptomatic rectal CT with azithromycin rather than doxycycline due to the relative simplicity of a single-dose regimen, although this varies geographically across the US [6]. The CDC's treatment recommendation is extrapolated from studies of azithromycin and doxycycline for the treatment of urogenital CT, but doxycycline may be more effective than azithromycin for the treatment of rectal CT. A well designed and conducted trial comparing the efficacy of the two recommended treatments could inform CDC's STD Treatment Guidelines for chlamydia in MSM and clinical practice.

2.2 Rationale

There are several possible explanations why doxycycline could be superior to azithromycin in the treatment of rectal CT. First, older randomized studies of azithromycin vs. doxycycline were limited to genital CT infections, while rectal CT may differ from genital CT infections due to host-microbial interactions. A study of chlamydial infection in mice found that doses of azithromycin that cured genital infections were ineffectual in eradicating gastrointestinal (GI) infections. This occurred despite comparable levels of azithromycin in both anatomic tracts. In contrast, doxycycline had similar efficacy in curing GI and genital tract infections [7]. Second, some strains of CT may have evolved to be less susceptible to azithromycin. Although azithromycin resistance among CT has never been conclusively demonstrated, evolution of antimicrobial resistance remains a possibility. Third, LGV, due to infection with L-serovar strains of CT, differentially causes proctitis, and some studies suggest that LGV is under-detected [8]. Treatment with a single dose of azithromycin may be less effective than a 7-day regimen of doxycycline in the treatment of undetected LGV. Although these factors could explain the

consistent findings in observational studies that doxycycline is superior to azithromycin, residual confounding remains a possible explanation. To date, only non-randomized retrospective studies have compared the effectiveness of doxycycline and azithromycin for the treatment of rectal CT [9]. Two potential explanations for the observed differences in observational studies include differential clinician prescription of azithromycin and doxycycline and different sexual behavior in patients who receive a single dose of medication vs. a 7-day course of medication. A placebo-blinded, randomized controlled trial is necessary to definitively compare the clinical efficacy of azithromycin vs. doxycycline for the treatment of rectal CT.

We hypothesize that doxycycline will be more effective than azithromycin in achieving microbiologic cure of rectal CT. To test this, we will screen and enroll MSM diagnosed with rectal CT into a randomized, double-blinded, placebo-controlled trial of azithromycin vs. doxycycline. The primary study outcome will be microbiologic cure (negative rectal CT NAAT result) 28 days after initiation of treatment.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Subjects will be treated with one of two commonly used, FDA-approved, first-line treatments for chlamydial infection. Risks to subjects will generally be similar to those associated with standard therapy for chlamydial infections and could include abdominal pain, allergic reaction, rash, nausea, vomiting, diarrhea, photosensitivity, dysphasia, or other unforeseen events.

The amount of lactose monohydrate that will be used for over-encapsulation and placebo is less than the amount necessary to cause lactose intolerance symptoms in those with lactose intolerance. Some subjects may experience mild bloating.

Potential risks due to collection of study rectal swabs may include temporary physical discomfort.

The study procedures may inconvenience or cause discomfort in subjects but will not add any substantial risk to health. Information concerning subjects' sexual history may provoke some minor psychological or emotional stress when requested.

Participation in research may involve a loss of privacy. Subject records will be kept as confidential as possible under the law. Individual identity will not be used in any reports or publications resulting from this trial.

2.3.2 Known Potential Benefits

Subjects in this trial may benefit from additional clinical care and testing provided at Days 15 and 29. Society will benefit from knowledge about the most effective treatment for rectal CT.

3 OBJECTIVES

3.1 Study Objectives

3.1.1 Primary Objective

- To compare the efficacy of azithromycin vs. doxycycline for treatment of rectal CT infection in MSM based on microbiologic cure (negative NAAT) at Day 29

3.1.2 Secondary Objectives

- To assess the effect of LGV infection on microbiologic cure in MSM with rectal CT at Days 15 and 29
- To compare the efficacy of azithromycin vs. doxycycline for treatment of rectal CT in MSM based on microbiologic cure at Day 15

3.1.3 Exploratory Objective

- To assess the effect of HIV status, adherence to study drug, antacid medication use, and symptomatic status on microbiologic cure at Day 29

3.2 Study Outcome Measures

3.2.1 Primary Outcome Measure

- The proportion of subjects with microbiologic cure in each study arm at Day 29

3.2.2 Secondary Outcome Measures

- The proportion of subjects with microbiologic cure in each study arm at Days 15 and 29 within subgroups defined by LGV infection at baseline
- The proportion of subjects with microbiologic cure in each study arm at Day 15

3.2.3 Exploratory Outcome Measure

- The proportion of subjects with microbiologic cure in each study arm at Day 29 within separate subgroups defined by HIV status at baseline, adherence to study drug, antacid medication use, and symptomatic status

4 STUDY DESIGN

This is a Phase 4, multi-center, randomized, double-blinded, placebo-controlled trial to compare the efficacy of azithromycin (Arm 1) vs. doxycycline (Arm 2) administered per CDC's STD Treatment Guidelines for rectal CT in MSM. Subjects will be males aged ≥18 years with a microbiologically confirmed diagnosis of rectal CT and at least one male sex partner in the past 12 months. Two types of subjects will be recruited:

- Subjects who have a confirmed positive rectal CT NAAT result detected through standard clinical screening and have not received treatment will be offered initial information about the trial and, if consent is provided, will be screened for eligibility.
- Subjects identified as having high risk for rectal chlamydia, defined as either a) having known contact to chlamydia and reporting receptive anal intercourse in the past 30 days or b) otherwise identified by a clinician as having an indication for empiric treatment. If pre-screened potentially eligible (no antibiotics in the past 21 days), they will be asked to consent to defer empiric treatment and to abstain from sex until their clinical NAAT results for CT and *N. gonorrhoeae* (GC) are available. Subjects who test positive for rectal CT and negative for GC will be asked to consent to continued study participation.

Subjects known to be HIV-positive will be included. For this trial, HIV status will be based on subject report. Subjects who have not been previously diagnosed with HIV and who have not recently tested negative for HIV will be offered HIV testing per the standard clinical practice at each site. The trial will be conducted at two sites in the US and will enroll up to 274 total subjects to achieve 246 subjects who contribute to the primary analysis.

Eligible subjects who consent to participate will be enrolled in the trial, which involves three scheduled visits over a 29-day period (Screening/Enrollment on Day 1, Follow-up Visits on Days 15 and 29). At Visit 1, after subjects provide informed consent and are determined to be eligible, study staff will collect baseline information on the subject's current rectal symptoms, sexual, STD and HIV history, and clinical and laboratory findings. Subjects will provide one baseline rectal swab for CT and LGV testing (NAAT) (clinician- or self-collected, to be obtained according to local clinic standard operating procedures (SOPs)). Subjects who consent to collection and storage of swabs for future use will have two additional swabs collected by the clinician (one for storage in culture media and one frozen). All subjects will be counseled on study drug side effects, randomized (1:1) to receive azithromycin and placebo doxycycline (Arm 1) or doxycycline and placebo azithromycin (Arm 2), and administered the full dose of azithromycin (or placebo) plus one dose of doxycycline (or placebo) in the clinic. Research staff will attempt to recruit the partners of enrolled subjects for screening visits by offering enrolled subjects the option to deliver information cards to their partners.

At Visit 1, subjects will be informed of the option to self-collect Visit 2 and/or Visit 3 swabs outside of the clinic, mail the specimens to the laboratory, and receive follow-up phone calls at

those time points rather than return to the clinic (hereafter referred to as the mail-in option). Subjects who opt for the mail-in option will receive supplies for specimen collection kit and instructions.

Adherence to the study drugs will be assessed by the observation of the subject taking the initial doses at Visit 1 (or at retreatment within 48 hours, if applicable), subject interview at follow-up visit or phone interview, and pill count from returned study drug (if any) if the subject returns to the clinic for follow-up visits. At Visits 2 and 3, subjects will be asked to provide information about rectal symptoms, serious adverse events (SAEs), concomitant medication use, and interim sexual, STD, and HIV history. Subjects who return to the clinic will have one rectal swab collected (clinician- or self-collected according to the subject's preference) for CT and LGV testing (NAAT).Those who consent to collection and storage of swabs for future use and return to the clinic for follow-up visits will have two additional swabs collected by the clinician (one for storage in culture media and one frozen) at each visit. Subjects who choose to self-collect rectal NAAT swabs outside the clinic will complete follow-up data collection by phone and no future use swabs will be collected at follow-up visits.

Subjects with a positive or indeterminate rectal CT NAAT result from their final study visit (i.e., Visit 3 or Early Termination Visit) will be contacted and referred to a care provider in the general clinic for appropriate treatment. At that appointment, those subjects will learn which treatment they received during the trial.

Oversight will be provided by a Data and Safety Monitoring Board (DSMB) that will review data at specified times during the course of the study for subject and overall study progress (as defined in the DSMB Charter).

All laboratory testing performed after informed consent and enrollment will include NAAT for CT by Aptima Combo 2® Assay (Hologic, Inc., San Diego, CA, USA) and polymerase chain reaction (PCR) assay for LGV at University of Washington (UW) Global Health STI Laboratory.

The duration of the trial for each subject will be 29 days. Enrollment and follow-up are expected to be completed in 22 months. For additional details on the study procedures, evaluations, and schedule, see Sections 7 and 8 and Appendix A.

5 STUDY ENROLLMENT AND WITHDRAWAL

To achieve 246 subjects eligible for the primary analysis, up to 274 males aged ≥18 years who meet all inclusion criteria and no exclusion criteria will be enrolled. We will screen subjects who have a positive rectal CT NAAT result as detected through standard clinical testing. Research staff will attempt to recruit sexual partners of enrolled subjects for study screening by offering information cards to enrolled subjects to distribute to their partners. Subjects may be recruited from STI clinics, HIV clinics, primary care clinics, clinics serving LGBT patients, community-based STI screening sites, and public health partner services. To enhance recruitment and retention, sites may seek IRB permission to contact potential subjects by phone, text messaging, and/or email as appropriate.

5.1 Subject Inclusion Criteria

Subjects eligible to enroll in this trial must meet all inclusion criteria:

1. Willing and able to understand and provide written informed consent before initiation of any study procedures
2. Willing and able to comply with planned study procedures for all study visits
3. Male sex at birth and aged ≥18 years with valid contact information
4. At least one male sex partner (oral or anal) in the past 12 months
5. Untreated rectal CT diagnosed by a positive NAAT result
6. Willingness to abstain from condomless receptive anal sex during the trial
7. Willingness to complete a 7-day study drug regimen

5.2 Subject Exclusion Criteria

Subjects eligible to enroll in this trial must not meet any exclusion criteria:

1. Current clinical diagnosis of acute proctitis per the CDC's 2015 STD Treatment Guidelines: symptoms of anorectal pain, tenesmus, and/or rectal discharge with anoscopy findings confirming inflammation
2. Concomitant untreated gonorrhea (rectal, pharyngeal, or urethral) or known exposure to gonorrhea in the time between CT testing and study enrollment
3. Clinical diagnosis of concomitant untreated primary or secondary syphilis
4. Known allergy to tetracyclines or macrolides
5. Received antimicrobial therapy active against *C. trachomatis* within 21 days of positive rectal CT NAAT result, or between the positive CT NAAT result and study enrollment*

   *This includes subjects treated empirically on the day of testing due to known exposure to gonorrhea or chlamydia, as well as enrollment in another study using

antimicrobial therapy active against *C. trachomatis,* or planned enrollment in such a study during their time in this trial. Specifically, use of the following antibiotics is an exclusion criterion: azithromycin and other macrolides, doxycycline and related tetra- or glycylcyclines, fluoroquinolones, rifampin, quinupristin-dalfopristin, and linezolid.

6. Plans to move to another location that would preclude study follow-up appointments in clinic or by mail-in in the next 30 days
7. Use of any investigational drug contraindicated to treatment with azithromycin or doxycycline within 7 days before enrollment
8. Previous enrollment in this trial
9. Any other condition that, in the opinion of the investigator, would interfere with participation in the trial

5.3 Treatment Assignment Procedures

5.3.1 Randomization Procedures

Subjects will be randomized 1:1 to receive one of two active treatments: azithromycin 250 mg x 4 orally as a single dose of 1 gram (Arm 1) or doxycycline hyclate 100 mg orally twice daily for 7 days (Arm 2).

The list of randomized treatment assignments will be prepared by statisticians at the Statistical and Data Coordinating Center (SDCC) and included in the enrollment module of the Emmes Corporation's Internet Data Entry System (IDES). Advantage eClinical® will assign each subject to a blinded treatment number from the list after demographic and eligibility data have been entered. Each site will have a supply of blinded study drug kits pre-labeled with treatment numbers, each containing sufficient doses to treat a subject for 7 days. Once a subject is assigned a treatment number, the corresponding kit will be distributed to the subject.

Instructions for using the enrollment module are included in the IDES User's Guide. Manual back-up randomization procedures are provided in the Manual of Procedures (MOP) for use in case the site temporarily loses Internet access, or the online enrollment system is unavailable.

The trial will use a site-stratified, permuted, blocked randomization scheme. Permuted blocked randomization is used to avoid the potential for serious imbalance in the number of subjects assigned to each group, which can occur in simple randomization procedures.

5.3.2 Masking Procedures

Subjects, the study staff who dispense study drug and perform study assessments after study drug administration, data entry personnel at the sites, and laboratory personnel will be blinded

to treatment assignment. The DSMB will receive efficacy data in aggregate and presented by treatment group, but without the treatment group identified. The DSMB may request to be completely unblinded to individual study drug assignments, as needed, to adequately assess SAEs. Refer to the MOP for unblinding procedures.

Study drug will be prepared at the UW Harborview Medical Center (HMC) Investigational Drug Services (IDS) in numbered, placebo-controlled kits. All kits will look identical and contain an identical number of pills. Emmes will provide an unblinded list identifying the active drug in each kit to the UW HMC IDS staff responsible for preparing study drug kits. Clinicians, investigators, and all blinded staff will not have access to a list of treatment assignments received until after the trial has ended and analysis is completed.

For any subjects who have a positive or indeterminate rectal CT NAAT result from their final study visit (i.e., Visit 3 or an Early Termination Visit), a designated unblinded individual at each site will have access to an unblinded treatment report that indicates the actual treatment received, which will be disclosed to the subject at an appointment with a care provider in the general clinic.

5.3.3 Reasons for Withdrawal

Subjects may voluntarily withdraw their consent for further study participation at any time and for any reason without penalty or prejudice to future medical care. Subjects may be withdrawn from further study participation for the following reasons:

- Medical disease or condition, or any new clinical finding for which continued participation, in the opinion of the site principal investigator (PI) or appropriate sub-investigator, would compromise the safety of the subject, interfere with the subject's successful completion of the trial, or interfere with the evaluation of responses
- As deemed necessary by the site PI or appropriate sub-investigator for noncompliance or other reason
- Termination of the trial
- The subject vomits within 2 hours of the initial dose and is not re-dosed within 48 hours
- The subject vomits within 2 hours of re-dosing azithromycin (or placebo) plus one doxycycline (or placebo) capsule

Subjects may also voluntarily discontinue receiving any study intervention for any reason. An investigator may also discontinue a subject from receiving further study interventions.

Withdrawal of subjects from analysis populations is discussed in Section 10.

5.3.4 Handling of Withdrawals

Subjects who withdraw or are lost to follow-up after signing the informed consent form (ICF), randomization, and receipt of study drug will not be replaced. Subjects who withdraw consent after signing the ICF and randomization but before receipt of study drug may be replaced.

Subjects who withdraw their consent from further study participation will not continue any study procedures and will no longer be contacted for follow-up. Subjects who are withdrawn from further study participation by the site PI or appropriate sub-investigator for any reason will not continue study procedures. However, if withdrawn after receiving at least one dose of study drug, subjects will be encouraged to complete the Early Termination Visit (see Section 7.4), including safety and efficacy evaluations.

If symptoms of an SAE are continuing at the end of study participation, the subject will be given appropriate care under medical supervision outside of the trial and followed until the SAE is resolved or until the subject's condition becomes stable.

If subjects fail to appear for a follow-up visit, extensive effort (e.g., three documented contact attempts via phone calls, emails, etc., made on separate occasions and followed by a certified letter) will be made to locate or recall them or at least to determine their health status. Subjects who cannot be located after extensive effort will no longer be contacted for follow-up. These efforts will be documented in the subject's records.

5.3.5 Termination of Study

Although the study sponsor has every intention of completing the trial, the sponsor reserves the right to terminate the trial at any time for clinical or administrative reasons. Reasons for study termination may include, but are not limited to, the DSMB's recommendation or DMID's discretion.

6 STUDY INTERVENTION/DRUGS

6.1 Study Drug Description

Azithromycin and doxycycline are FDA-approved in the US for the treatment of CT and other infections. Azithromycin monohydrate is a macrolide antibacterial drug for oral administration. Doxycycline hyclate is an antibacterial drug synthetically derived from oxytetracycline for oral administration.

6.1.1 Acquisition

Azithromycin 250-mg generic tablets, doxycycline 100-mg generic capsules, and placebo capsules will be purchased in bulk by UW HMC IDS, which will prepare over-encapsulated active azithromycin tablets and active doxycycline capsules that appear identical to placebo azithromycin capsules and placebo doxycycline capsules containing lactose monohydrate. Lactose monohydrate will be used to over-encapsulated active azithromycin tablets and active doxycycline capsules, and to fill placebo capsules.

UW HMC IDS will package all capsules in individual, blinded, placebo-controlled study drug kits. Each kit will include two properly-labeled standard prescription vials containing either active azithromycin and placebo doxycycline, or active doxycycline and placebo azithromycin. UW HMC IDS will over-encapsulate, package, and label the kits according to the randomized treatment assignment list for each site and applicable regulatory requirements, and will transfer them to each site upon DMID's approval.

6.1.2 Formulation, Packaging, and Labeling

Active azithromycin
Azithromycin will be supplied as a 250-mg tablet. Each tablet will be placed in an opaque purple size 00 gelatin capsule and overfilled with lactose monohydrate. Four of these capsules will be placed in a properly-labeled prescription vial.

Placebo azithromycin
Each placebo azithromycin capsule will be filled with lactose monohydrate only and will appear identical to the capsule containing active azithromycin. Four of these capsules will be placed in a properly-labeled prescription vial.

Active doxycycline
Doxycycline will be supplied as a 100-mg capsule. Each capsule will be placed in an opaque purple size 00 gelatin capsule and overfilled with lactose monohydrate. Fourteen of these capsules will be placed in a properly-labeled prescription vial.

Placebo doxycycline
Each placebo doxycycline capsule will be filled with lactose monohydrate only and will appear identical to the capsule containing active doxycycline. Fourteen of these capsules will be placed in a properly-labeled prescription vial.

UW HMC IDS will prepare blinded placebo-controlled study drug kits. Each kit will include two properly-labeled prescription vials containing either four active azithromycin 250 mg capsules and 14 placebo doxycycline capsules, or four placebo azithromycin capsules and 14 active doxycycline 100 mg capsules. The two vials will be placed in a manila envelope, labeled with the treatment number, and allocated according to the randomized treatment assignment list generated by Emmes.

6.1.3 Study Drug Storage and Stability

Study drugs are stable at room temperature and will be stored at 15-30°C (59-86°F).

All study drugs will have a 6-month expiration from the date of over-encapsulation.

6.2 Dosage, Preparation and Administration of Study Drugs

A site Research Pharmacist may be delegated the responsibility of study drug dispensation, must be a licensed registered pharmacist, and is the preferred healthcare practitioner to be delegated this activity. If a Research Pharmacist is not available, a physician, nurse practitioner, physician assistant, registered nurse, or other authorized healthcare practitioner who is a member of the clinical study staff may be delegated to dispense study drug. These personnel must be licensed, trained, and qualified to prepare investigational study drugs and must be authorized to dispense study drug under state and local rules and regulations.

Subjects will be randomized to one of two treatment assignments:

- Azithromycin 250 mg x 4 (1 gram) orally as a single dose plus placebo doxycycline x 1 orally twice daily for 7 days (14 capsules total)

- Doxycycline 100 mg x 1 orally twice daily for 7 days (14 capsules total) plus placebo azithromycin x 4 orally as a single dose

The study clinician or designee will obtain the study drug kit corresponding to the subject's randomized treatment assignment. Each kit will contain two vials of study drugs. Packaging is described in Section 6.1.2 and study design and study arms are described in Section 4.

Study staff will instruct all subjects to take four azithromycin 250 mg capsules (or placebo) as a single dose plus one doxycycline 100 mg capsule (or placebo) at the end of the enrollment visit

(Day 1), observing these doses before subjects leave the clinic. Study staff will provide instructions for continued twice-daily doxycycline (or placebo) for 7 days to complete 14 doses. Subjects will be asked to bring the vial of doxycycline (or placebo) back to the clinic at Visit 2.

A subject who vomits the first dose of azithromycin (or placebo) and one doxycycline capsule (or placebo) within 2 hours of ingestion will be asked to return to the study clinic within 48 hours of the initial dose for re-treatment. Refer to the MOP for re-treatment procedures. Subjects who vomit within 2 hours of re-treatment will be withdrawn from the trial and treated per routine standard of care.

A subject who loses or damages the vial of doxycycline (or placebo) for continued twice-daily dosing will be asked to return to clinic as soon as possible to receive replacement study drug. At that time, the study clinician or designee will provide the subject with the appropriate number of doxycycline (or placebo) capsules to complete all remaining doses. Refer to the MOP for replacement study drug procedures. Subjects will be asked to bring the vial of doxycycline (or placebo) back to the clinic at Visit 2.

6.3 Accountability Procedures for the Study Drug Kits

UW HMC IDS will ship study drug kits to each site, where the site PI will be responsible for their receipt, storage, distribution, disposition, and accountability. The site PI may delegate these responsibilities to a site Research Pharmacist or designee. All kits, whether administered, unused, discarded, or expired, must be documented on the appropriate study drug accountability record or dispensing log.

The final disposition of study drug is described in the MOP.

6.4 Assessment of Subject Compliance with Study Drug

Subject adherence to study treatment will be assessed by the observation of the subject taking the dose of azithromycin (or placebo) and one doxycycline capsule (or placebo) at Visit 1 (or at retreatment within 48 hours, if applicable) as well as subject interview at follow-up and count of the number of doxycycline (or placebo) pills returned (if any) for those who return to clinic for follow-up visits. Adherence will be recorded on the appropriate data collection form (DCF). Subjects who voluntarily discontinue study drug before completing the dosing regimen will remain in the trial and be followed for safety and efficacy.

6.5 Concomitant Medications/Treatments

Administration of any medications will be recorded on the appropriate DCF. Concomitant medications will include all medications taken 21 days before initiating study treatment through

Visit 3 or early termination, whichever occurs first. Prescription and over-the-counter (OTC) medications (including antacids) will be included, as well as, herbs, vitamins, and other supplements. Previously recorded medications will be updated as appropriate.

Subjects who have received study drug and are subsequently diagnosed with a concomitant infection that requires systemic antibiotics will receive treatment according to the local clinic's standard clinical practice, which will avoid antibiotics active against CT if a suitable alternative is available. Subjects who receive antibiotics active against CT after study drug administration will remain in the trial and followed for safety and efficacy. The medications that are prohibited for study eligibility in Section 5.2 are also prohibited throughout study participation.

7 STUDY SCHEDULE

Study visit information is listed in this section, Section 8, and Appendix A. Further instructions are described in the protocol-specific MOP.

7.1 Visit 0 – Screening Visit (Day -30 to -1)

- Sites will follow their site-specific instructions for approaching and pre-screening potential subjects for the screening visit. Potential subjects aged ≥18 years seeking care in participating clinics will be pre-screened for preliminary study eligibility if they are considered high risk for rectal chlamydia and have not taken antibiotics in the past 21 days. High risk is defined as a) having known contact to chlamydia and receptive anal intercourse in the past 30 days or b) identified by a clinician as having an indication for empiric treatment.

- Potential subjects who meet these criteria will be provided with a description of the trial (purpose and study procedures) and asked to consent to defer empiric treatment and abstain from sex of any kind (oral, anal or vaginal) until their clinical NAAT results for CT and GC are available. Consent will be obtained by asking the individual to read and sign the appropriate consent form. The ICF form will be signed prior to performing any study procedures.

- Demographic information will be obtained by interview of the subject.

- A subset of eligibility criteria will be reviewed with the subject.

- Subject contact information for follow-up and study visit reminders will be collected.

- Subjects will be scheduled to return to clinic for Visit 1 when CT and GC NAAT test results are expected (i.e., based on the local lab test turnaround time).

AFTER VISIT 0 ENDS AND PRIOR TO VISIT 1

- Study staff will follow up on the results of clinical labs.

- Subjects who test positive for rectal CT and negative for GC will return for the Enrollment Visit, which is scheduled at the end of the Screening Visit.

- Subjects whose clinical NAAT tests return with any ineligible results (i.e., CT positive, GC positive; CT negative, GC negative; CT negative, GC positive) will be informed that they are no longer eligible. Study staff will arrange for and ensure appropriate treatment based on standard clinical practices at each site.

7.2 Visit 1 – Screening and Enrollment/Baseline Visit, Day 1

- Sites will follow their site-specific instructions for approaching and pre-screening MSM for this trial. Two types of subjects will be recruited:
    - High risk MSM who consented to deferring empiric treatment at the screening visit and NAAT test results return positive for CT and negative for GC.
    - MSM aged ≥18 years seeking care in participating clinics who have had an untreated positive rectal CT NAAT result detected through standard clinical screening.
- Individuals who meet either of these criteria will be provided with a description of the trial (purpose and study procedures) and asked to read and sign the appropriate ICF. The ICF will be signed before performing any screening or study procedures.
- Demographic information will be obtained or, if applicable, confirmed (i.e., if previously collected at screening) by interview of the subject.
- Eligibility criteria will be reviewed with the subject.
- Untreated positive rectal CT NAAT result will be confirmed by laboratory report or electronic medical record (EMR).
- Sexual and STD history for the past 60 days will be collected.
- HIV testing and treatment history will be obtained by interview of the subject.
- All prior medications taken in the last 21 days before initiating study drug will be recorded on the appropriate DCF.
- The presence or absence of individual rectal symptoms (i.e., pain, irritation, tenesmus, discharge, bleeding) and inguinal lymphadenopathy will be documented. The investigator will state whether the rectal sign or symptom is related to rectal CT and indicate if the subject was symptomatic or asymptomatic for rectal CT.
- A targeted physical examination of the inguinal lymph nodes will be performed by a qualified study clinician and, if indicated based on subject report of symptoms, a more extensive physical exam of the genitals and anorectum will be performed, and documented.
- Subjects will be asked to choose between returning to the clinic for follow-up visits and/or mailing in self-collected swabs and completing a phone call for data collection.
- All subjects will provide one rectal swab for baseline CT NAAT (clinician- or self-collected). Two additional rectal swabs for storage and future use will be collected by a clinician from all consenting subjects at baseline.

- Subjects will be registered in Advantage eClinical® and randomly assigned to a treatment number corresponding to Arm 1 or Arm 2.

- Study drug will be provided to the subject per randomized assignment in a prepared study drug kit along with dosing instructions.

- Subjects will be observed taking four 250-mg azithromycin capsules (or placebo) as a single dose plus one doxycycline hyclate 100 mg capsule (or placebo), and treatment administration will be documented. Study staff will instruct subjects to continue twice-daily doxycycline (or placebo) for 7 days to complete 14 doses. If a subject vomits the first dose of azithromycin (or placebo) and one doxycycline capsule (or placebo) within 2 hours of ingestion, a repeat dose is allowed in the study clinic within 48 hours of the initial dose. Re-treatment procedures are described in Sections 6.2 and 7.5.

- Subjects will be reminded to abstain from receptive anal sex or use condoms during receptive anal sex for the duration of their participation in the trial.

- Subjects will be scheduled to return to clinic or to complete a phone call, based on the subject's preference, for Visit 2 approximately 14 days (i.e., 12-18 days, depending on staff and subject availability) after the first dose of study drug. Subject contact information for follow-up and study visit reminders will be collected.

- Subjects who choose the mail-in option for Visits 2 and/or 3 will be given materials to self-collect rectal swabs for NAAT testing and mail them in. Refer to Section 8.3.2 for further information about specimen preparation, handling, and shipping.

- Subjects will be encouraged to refer sexual partners to the study.

7.3 Visit 2 – Follow-up Visit, Day 15 (Day 12-18)

- The following information will be collected in person or in a telephone call with study personnel according to the subject's choice to return to the clinic for visits or mail in self-collected swabs, respectively:

    - Interim sexual and STD history since the last study visit will be collected.

    - Interim HIV testing and treatment history will be reviewed and updated as appropriate.

    - All concomitant medications taken since the last study visit will be recorded on the appropriate DCF. Prior medications will be updated as appropriate.

    - The subject's self-reported study drug adherence will be recorded. If any study drug doses were not taken, the subject's self-reported reason(s) for nonadherence (e.g., forgetfulness, drug intolerance) will be recorded. Subjects who report nonadherence due to intolerance will be asked about adverse effect(s) (e.g., nausea, vomiting, diarrhea, dysphasia, abdominal pain, rash).

        - For subjects who return to clinic, study drug vials will be collected (if returned) and the number of remaining pills will be counted (if any) and recorded.

    - The presence or absence of individual rectal symptoms (i.e., pain, irritation, tenesmus, discharge, bleeding) and inguinal lymphadenopathy will be documented. The investigator will assess whether the rectal sign or symptom reported by the subject is related to rectal CT and indicate if the subject was symptomatic or asymptomatic for rectal CT if a rectal sign or symptom was reported.

    - Study personnel will discuss with subjects and assess and record all SAEs.

- For subjects who complete follow-up in the clinic, a targeted physical examination (genitals, inguinal lymph nodes, and anorectum) will be performed by a qualified study clinician if applicable based on subject-reported symptoms, and documented. Subjects who complete follow-up by telephone may be asked to come into the clinic for examination if they report symptoms.

- For subjects who return to the clinic, one rectal swab will be collected for CT NAAT (clinician- or self-collected). Two additional rectal swabs will be collected by the clinician from consenting subjects for storage and future use. Subjects who choose the mail-in option will self-collect one rectal swab to send to the laboratory for CT NAAT.

- Subjects will be reminded to abstain from receptive anal sex or use condoms during receptive anal sex for the duration of the trial.

- Subjects will be scheduled to return to clinic or to complete a phone call, based on the subject's preference, for Visit 3 approximately 28 days (i.e., 25-31 days, depending on staff and subject availability) after the first dose of study drug. Subject contact information and preferences will be updated accordingly.

- Subjects will be encouraged to refer sexual partners to the study.

7.4 Visit 3 – Final Visit, Day 29 (Day 25-31)

- The following information will be collected in person or in a telephone call with study personnel according to the subject's choice to return to the clinic for visits or mail in self-collected swabs, respectively:

    - Interim sexual and STD history since the last study visit will be collected.

    - Interim HIV testing and treatment history since the last study visit will be reviewed and updated as appropriate.

    - All concomitant medications taken since the last study visit will be recorded on

the appropriate DCF. Prior medications will be updated as appropriate.

- The presence or absence of individual rectal symptoms (i.e., pain, irritation, tenesmus, discharge, bleeding) and inguinal lymphadenopathy will be documented. The investigator will assess whether the rectal sign or symptom reported by the subject is related to rectal CT and indicate if the subject was symptomatic or asymptomatic for rectal CT if a rectal sign or symptom was reported. Subjects with symptoms will be referred to the general clinic for appropriate care.

- Study personnel will discuss with subjects and assess and record all SAEs. Previously recorded SAEs will be updated as appropriate. Study staff will ensure any subject with an ongoing SAE is referred for appropriate care.

- If not already done at Visit 2 (or at an Unscheduled Visit if Visit 2 was missed or the assessment was not conducted), the subject's self-reported study drug adherence will be recorded. If any study drug doses were not taken, the subject's self-reported reason(s) for nonadherence (e.g., forgetfulness, drug intolerance) will be recorded. Subjects who report nonadherence due to intolerance will be asked about adverse effect(s) (e.g., nausea, vomiting, diarrhea, dysphasia, abdominal pain, rash).

    - For subjects who return to clinic, study drug vials will be collected (if returned) and number of remaining pills will be counted (if any) and recorded.

- For subjects who complete follow-up in clinic, a targeted physical examination (genitals, inguinal lymph nodes, and anorectum) will be performed by a qualified study clinician if applicable based on subject-reported symptoms, and documented. Subjects who complete follow-up by telephone may be asked to come into the clinic for examination if they report symptoms.

- For subjects who return to the clinic, one rectal swab will be collected for CT NAAT (clinician- or self-collected). Two additional rectal swabs for storage and future use will be collected by the clinician from consenting subjects. Subjects who choose the mail-in option will self-collect one rectal swab for CT NAAT.

- Subjects will be encouraged to refer sexual partners to the study.

The following will occur if any subject has a positive or indeterminate rectal CT NAAT result from their final study visit (i.e., Visit 3 or Early Termination Visit):

- Study staff will notify subjects of the CT-positive or indeterminate result and refer them to a care provider in the general clinic for appropriate treatment per standard clinic care.

- Designated unblinded staff will determine the subject's treatment assignment via an unblinded treatment report and share that information with the subject at the general

clinic appointment.

7.5 Early Termination Visit

The final study visit assessments and electronic case report forms (eCRFs) (see Section 7.3) should be completed if possible at the end of each subject's participation in the trial if participation is terminated before Visit 3. If a subject withdraws between scheduled visits, the subject will be asked to come into the clinic to perform the Visit 3 assessments. If adherence has not yet been assessed, study drug vials will be collected (if returned) and number of pills remaining counted (if any), and subject interview of study drug adherence will be recorded. Subjects who have a positive or indeterminate rectal CT NAAT result will be referred to a care provider in the general clinic for appropriate standard-of-care treatment and will learn their study drug assignment at that time.

7.6 Unscheduled Visit

Subjects will be permitted to return for unscheduled visits in the brief interval between enrollment and scheduled follow-up as needed to address (i) retreatment after vomited study drug, (ii) replacement of lost or damaged study drug, or (iii) other issues such as SAEs, continuing or new symptoms, etc., as they arise. All unscheduled visits and the reasons for them will be documented.

Retreatment after vomited study drug: If a subject vomits the first dose of azithromycin (or placebo) plus one doxycycline capsule (or placebo) within 2 hours of ingestion and returns to the clinic within 48 hours of the initial dose, the study clinician or designee will replace the initial dose for each respective treatment, observe these doses before the subject leaves the clinic, and document the treatment dispensed.

Replacement of lost or damaged study drug: If a subject loses or damages the vial of continued doxycycline (or placebo) for twice-daily dosing, the study clinician or designee will provide the remaining number of doxycycline (or placebo) capsules to the subject, and document the treatment dispensed.

Other issues: The following activities may be performed at the discretion of the site PI:

- Interim sexual and STD history since the last study visit will be collected.
- Interim HIV testing and treatment history since the last study visit will be reviewed and updated as appropriate.
- All concomitant medications taken since the last study visit will be recorded on the appropriate DCF. Prior medications will be updated as appropriate.
- If after the dosing period is complete and adherence has not yet been assessed, study drug vials will be collected (if returned), the number of remaining pills counted (if any), and the subject's study drug adherence recorded. If any study drug doses were not

taken, the subject's self-reported reason(s) for nonadherence (e.g., forgetfulness, drug intolerance) will be recorded. Subjects who report nonadherence due to intolerance will be asked about adverse effect(s) (e.g., nausea, vomiting, diarrhea, dysphasia, abdominal pain, rash).

- The presence or absence of individual rectal symptoms (i.e., pain, irritation, tenesmus, discharge, bleeding) and inguinal lymphadenopathy will be documented. The investigator will assess whether the rectal sign or symptom reported by the subject is related to rectal CT and indicate if the subject was symptomatic or asymptomatic for rectal CT if a rectal sign or symptom was reported.

- Study personnel will discuss with subjects and assess and record all SAEs. Previously recorded SAEs will be updated as appropriate.

- For subjects who return to the clinic, a targeted physical examination (genitals, inguinal lymph nodes, and anorectum), will be performed by a qualified study clinician if applicable based on subject-reported symptoms, and documented. Subjects who complete visit by telephone may be asked to come into the clinic for examination if they report symptoms.

- One rectal swab may be collected from all subjects for CT NAAT (clinician- or self-collected). Two additional rectal swabs for storage and future use may be collected by the clinician from consenting subjects.

- Subjects will be reminded to abstain from receptive anal sex or use condoms during receptive anal sex for the duration of the trial.

- Subject contact information and preferences will be reviewed and updated accordingly.

8 STUDY PROCEDURES/EVALUATIONS

8.1 Clinical Evaluations

Sexual and STD history, including number of male partners, condom-protected and condomless sex with new and previous partners, knowledge about whether partners were treated for chlamydia, receptive anal-oral contact, lubricant use, enema use, and any previous diagnoses of chlamydia, gonorrhea, syphilis, with approximate date of most recent infection for each, will be obtained by interview of the subjects at Visit 1. At follow-up visits, an interim sexual and STD history will be obtained by interview of the subjects, noting any changes since the previous visit and adherence to protocol requirements (i.e., abstinence from receptive anal sex or use of condoms during receptive anal sex for the duration of the trial).

HIV testing and treatment history, including HIV status (positive, negative, or unknown), date of last HIV test (month and year), and antiretroviral treatment status (taking or not taking antiretroviral therapy) will be obtained by interview of the subjects at Visit 1 and will be updated at each clinic visit.

A concomitant medications history will include a review of all current medications, and medications taken 21 days before initiating study drug. Prescription (including antibiotics) and OTC medications (including antacids) will be included as well as vitamins, herbs, and supplements. Assessment of eligibility will also include a review of all permitted and prohibited medications per Section 5.

Self-reported reason(s) for nonadherence will be recorded at follow-up if any doses of study drug were not taken. If drug intolerance is reported as a reason for nonadherence, symptoms of intolerance will be assessed and recorded.

At each study visit, the presence or absence of individual rectal symptoms (i.e., pain, irritation, tenesmus, discharge, bleeding) and inguinal lymphadenopathy will be obtained by interview of the subject and documented. The investigator will assess whether the reported rectal sign or symptom is related to rectal CT and indicate if the subject was symptomatic or asymptomatic for rectal CT at that visit as determined by the evaluation of reported rectal symptoms and inguinal lymphadenopathy.

At baseline, a targeted physical examination of the inguinal lymph nodes will be completed and, if applicable based on symptom review, a more extensive physical exam of the genitals and anorectum will be performed. For subjects who complete follow-up in the clinic, a targeted physical examination (genitals, inguinal lymph nodes, and anorectum) will be performed if applicable based on subject-reported symptoms. All physical examinations will be performed by a qualified study clinician.

8.2 Laboratory Evaluations

8.2.1 Laboratory Evaluations

Diagnostic laboratory tests for rectal CT and LGV will be performed at the UW Global Health STI Laboratory using rectal swabs collected at each study visit. Instructions for obtaining rectal swab specimens for these assessments are outlined in the MOP.

Aptima Combo 2® for Diagnosis of CT

Aptima Combo 2® NAAT will be performed on rectal swab specimens per the manufacturer's instructions to diagnose CT.

8.2.2 Special Assays or Procedures

Molecular Analysis of *C. trachomatis* for Determination of LGV

Multiplex PCR will be performed only on positive CT NAAT specimens to identify LGV strains of CT.

8.2.3 Specimen Preparation, Handling, Storage, and Shipping

8.2.3.1 Instructions for Specimen Preparation, Handling, and Storage

The UW will assemble and provide sites with standardized Aptima collection kits to be given to subjects who choose to the mail-in option for follow-up visits. Refer to the MOP for further information about packaging, transport, and storage of Aptima collection kits.

Specimen preparation, handling, and storage will be done according to local clinic SOPs. Additional details can be found in the protocol-specific MOP.

8.2.3.2 Specimen Shipment

Specimens for CT NAAT collected at or outside the clinic as well as specimens for possible future use will be shipped to the UW Global Health STI Laboratory at the following address, according to all applicable International Air Transport Association (IATA) requirements:

University of Washington Global Health STI Laboratory

Harborview Medical Center

[redacted]

Additional details can be found in the protocol-specific MOP.

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

Due to the safety profile of both drugs used in this trial, only SAEs (not non-serious AEs) that occur during the subject's participation in the trial will be collected.

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

9.2.1 Serious Adverse Events

Serious Adverse Event (SAE):

ICH E6 defines an AE as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care.

An AE or suspected adverse reaction 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*,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- important medical events that may not result in death, be life-threatening, or require hospitalizations 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 the development of drug dependency or drug abuse.

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

All SAEs will be:

- Assessed for severity and relationship to study drug and alternate etiology (if not related to study drug) by a licensed study physician.
- Recorded on the appropriate SAE form and eCRF.
- Followed through resolution by a licensed study physician.
- Reviewed and evaluated by DMID and reported to the DSMB (at one interim meeting and one final closeout meeting only, not *ad hoc*) and the IRBs.

Severity of Event: All SAEs will be assessed by the clinician using a protocol-defined grading system. For events not included in the protocol-defined grading system, the following guidelines will be used to quantify intensity.

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

Changes in the severity of an SAE should be documented to allow an assessment of the duration of the SAE at each level of intensity to be performed. SAEs characterized as intermittent require documentation of onset and duration of each episode.

Relationship to Study Drug: All SAEs must have their relationship to study drug assessed using the terms: related or not related. In a clinical trial, study drug must always be suspect. To help assess, the following guidelines are used.

- Related – There is a reasonable possibility that the study drug caused the SAE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study drug and the SAE.

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

9.2.2 Procedures to be Followed in the Event of Abnormal Clinical Findings

The site PI or appropriate sub-investigator is responsible for reporting all SAEs that are observed or reported during the trial, regardless of their relationship to study drug. SAEs or abnormal clinical findings will be documented, reported, and followed appropriately.

9.3 Reporting Procedures

9.3.1 Serious Adverse Events

SAEs will be followed until resolution even if this extends beyond the study reporting period. Resolution of an SAE 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, at the following address:

DMID Pharmacovigilance Group
Clinical Research Operations and Management Support (CROMS)
[redacted]

Other supporting documentation of the event may be requested by the DMID Pharmacovigilance Group and should be provided as soon as possible.

The DMID Medical Monitor and clinical protocol 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 completion of the trial, if the investigator becomes aware of an SAE that is suspected to be related to study drug, the investigator will report the event to the DMID Pharmacovigilance Group.

9.4 Type and Duration of Follow-up of Subjects After Serious Adverse Events

SAEs will be followed from the time of study treatment through resolution even if this extends beyond the study reporting period (i.e., the Day 29 visit). Resolution of an SAE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

Follow-up procedures, evaluations, and outcomes will be recorded on the appropriate DCF.

9.5 Halting Rules

Due to the safety profile established by both approved drugs, the need for halting rules for safety outcomes is not deemed a requirement. Should the DMID Medical Monitor become aware of any highly unusual, unanticipated patterns of rare events, he will be able to stop enrollment and study treatments until the issue is fully resolved.

9.6 Oversight by DSMB

Oversight will be conducted by a DSMB, an independent group of experts that monitors subjects and study progress as outlined in the DSMB Charter and advises DMID appropriately. DSMB members will be separate and independent of study personnel participating in this trial; should not have scientific, financial, or other conflicts of interest related to this trial; and will have appropriate expertise to contribute to the interpretation of the data from this trial.

The DSMB will operate under the rules of a DMID-approved charter that will be written at the DSMB's organizational meeting. As defined in the charter, the DSMB will review data at specified times during the course of the study for subject and overall study progress. As an outcome of the efficacy review, the DSMB will make a recommendation as to the advisability of stopping the trial early (due to compelling evidence that one of the treatments is more effective) or proceeding with study enrollment, and to continue, modify, or terminate the trial.

DMID or the DSMB chair may convene the DSMB on an *ad hoc* basis if there are immediate concerns regarding observations during the trial. The DMID Medical Monitor will be responsible for reviewing SAEs in real time and determines if notification of the DSMB is required according to the protocol and the Charter.

10 STATISTICAL CONSIDERATIONS

10.1 Study Hypotheses

There is one planned formal test of hypothesis which compares azithromycin to doxycycline with respect to the primary efficacy outcome measure. The hypothesis test compares the proportion of subjects with microbiologic cure between treatment arms at Visit 3. The null hypothesis for the comparison is that there is no difference in proportions between treatment arms, with a two-sided alternative. The test will be conducted using a Pearson Chi-Square test at the 5% two-sided significance level.

10.2 Sample Size Considerations

The sample size is derived from power calculations for a two-staged group sequential design with one unblinded interim analysis of the primary outcome halfway through the trial and the final analysis after the trial has been completed.

O'Brien-Fleming boundaries will be used for the interim and final analyses to control the overall Type I error of the trial at 5%. The choice of O'Brien-Fleming is motivated by the desire to stop the trial early only if the interim difference in cure rates between treatment groups is large, and to continue in the presence of a moderate or small interim difference. For the calculations, it was assumed that the interim analysis will occur when 50% of the planned number of primary analysis-eligible subjects have been enrolled and followed through Day 29.

The sample size for the study was updated from the original target due to logistical and feasibility reasons. The enrollment target is 274 subjects. Based on previous prospective studies of MSM recruited from the PHSKC STD clinic [10-13], it is anticipated that at least 90% of enrolled subjects will be eligible for the primary analysis population; therefore, it is expected that 274 enrollments will lead to approximately 246 subjects eligible for the primary analysis.

Previously reported cure proportions have generally ranged 95-100% for doxycycline and 74-92% for azithromycin [14-20]. The 246 primary-analysis-eligible subjects along with the O'Brien Fleming boundaries will provide 75-80% power to detect a 10% difference in cure rates between treatments using conservative estimates of treatment-specific cure rates based on the literature (~95% cure rate for doxycycline and ~85% cure rate for azithromycin). The study will have more than 80% power to detect a 10% difference across a range of cure rates of doxycycline and azithromycin consistent with rates calculated in a meta-analysis of the efficacy of azithromycin and doxycycline for the treatment of rectal chlamydia infection [9]. See Table 1 below for power estimates.

Table 1: Power available to detect a 10% difference in cure proportions between treatments detectable with total sample size of N = 246 and interim analysis at N = 123

Cure Proportion		Power
Doxycycline	Azithromycin	
95%	85%	75%
96%	86%	79%
97%	87%	83%
98%	88%	87%
99%	89%	92%

As noted above, O'Brien Fleming boundaries are used to employ a conservative stopping rule at the interim analysis. Under a null hypothesis that the cure proportion of doxycycline and azithromycin are both 87%, the probability of stopping the trial at the interim analysis is less than 1%. Under an alternative that the cure proportions of doxycycline and azithromycin are 97% and 87%, respectively, the probability of stopping the trial at the interim analysis is 23%.

It is important to note that the exact number of subjects eligible for the primary analysis at the interim and final analyses may vary from 123 and 246, respectively. It is expected that the actual variations from the assumptions made in the power calculations will be small. The overall Type I error of the O'Brien-Fleming methodology with only one interim look is robust to small deviations in the timing of the interim analysis and the exact number of subjects at the final analysis, though the attained power may drop slightly below 80% [21, 22].

10.3 Planned Interim Analyses

10.3.1 Safety Review

The DSMB will review SAEs at the interim efficacy review (see below).

10.3.2 Efficacy Review

The DSMB will review a formal analysis of efficacy when approximately half (N=123) of subjects have contributed primary outcome measure data. At this time, an unblinded analysis of the

primary outcome measure will be performed by the unblinded statistical team and provided only to the DSMB (details will be provided in the Statistical Analysis Plan [SAP]). This interim analysis is intended to inform the DSMB's recommendation to the sponsor only whether the trial meets the criterion for stopping early (null hypothesis is or is not rejected).

10.4 Final Analysis Plan

A separate SAP document will be generated that will contain the details of the analyses. This section outlines the major components of the analyses.

10.4.1 Analysis Populations

10.4.1.1 Safety Analyses

Safety Population: This analysis population includes all randomized subjects who receive at least one dose of study drug.

10.4.1.2 Efficacy Analyses

Intent-to-Treat (ITT) Population: This analysis population includes all randomized subjects.

Complete Case (CC) Population: This analysis population includes all randomized subjects who meet all inclusion/exclusion criteria at enrollment, have a positive baseline rectal CT NAAT result, and have post-baseline microbiologic data available. For analyses at Day 15, microbiologic data must be available from the Day 15 visit. Likewise, for analyses at Day 29, microbiologic data must be available from the Day 29 visit.

The CC population will be the primary efficacy analysis population.

Per-Protocol (PP) Population: This analysis population includes all randomized subjects who meet all inclusion/exclusion criteria at enrollment, have a positive baseline rectal CT NAAT result, have post-baseline microbiologic data available, sufficiently adhere to the study drug regimen (defined below), and do not experience any of the following after enrollment and before a particular visit (Day 15 for analyses at Day 15, and Day 29 for analyses at Day 29):

- Receive treatment for a symptomatic STD other than CT
- Exposure to an STD
- Receive treatment with an antibiotic active against CT
- Have condomless receptive anal sex

For analyses at Day 15, microbiologic data must be available from the Day 15 visit. Likewise, for analyses at Day 29, microbiologic data must be available from the Day 29 visit.

A subject is considered sufficiently adherent with study treatment if he takes the initial dose of azithromycin (or placebo) and initial dose of doxycycline (or placebo) in the clinic (or at retreatment within 48 hours, if applicable) and at least 9 additional doses of doxycycline (or placebo) within 10 days (inclusive) of the initial completed dose (or of the completed retreatment dose, if applicable). Assessment of subject adherence to study treatment is described in Section 6.4.

Alternative definitions of compliance and analyses of adherence will be explored; details will be provided in the SAP.

Before unblinding, a blinded case review committee will review subjects with a reported concomitant infection/disease/procedure that may interfere with study drug, use of concomitant medications or products that may interfere with study drug, significant protocol deviations, and other events that may impact study drug effectiveness or study analyses. On a case-by-case basis, the case review committee will determine if each subject will be included in the PP population, if and when a subject should be censored or removed from PP analyses, and/or any other analytical requirements for the subject. The committee will be blinded to both treatment group and outcome status for each case.

10.4.1.3 Considerations for all Analyses

In the unlikely event of an error in randomization or study drug administration, subjects will be grouped by the formulation they actually received in Safety, CC, and PP analyses but will be grouped by their intended randomized assignment in ITT analyses.

Subjects who receive treatment with an antibiotic active against CT for any reason before a particular post-baseline visit (Day 15 for analyses at Day 15, and Day 29 for analyses at Day 29) will be included in ITT and CC analyses as microbiologic failures and reviewed by the blinded case committee for inclusion in PP analyses.

Other subgroup analyses may be performed; details will be provided in the SAP.

10.4.2 Baseline Characteristics

Baseline and demographic characteristics will be summarized overall and by treatment. For both continuous and categorical variables, appropriate summary statistics will be applied. For continuous variables, descriptive statistics will include the number of non-missing values, mean, standard deviation, median, minimum, and maximum. For categorical variables, descriptive statistics will include counts and percentages per category.

10.4.3 Safety Analysis Plan

Safety evaluations will be based on the incidence, severity, and type of SAEs. Safety variables will be tabulated and presented for all subjects in the Safety population, grouped by treatment.

SAEs will be coded by MedDRA® for preferred term and system organ class. The proportion of subjects with SAEs in aggregate, as well as by MedDRA® categories, will be computed. The number of SAEs will be reported by a detailed listing showing the type, MedDRA® coding, relevant dates (treatment dosing dates and SAE onset and resolution dates), severity, relatedness, and outcome for each SAE.

10.4.4 Efficacy Analysis Plan

10.4.4.1 Primary Efficacy Analysis

To compare the efficacy of azithromycin vs. doxycycline for treatment of rectal CT in MSM, the number and proportion of subjects with microbiologic cure at Visit 3 will be summarized overall and by treatment. The point estimates for the treatment-specific proportions and difference in proportions as well as corresponding 95% confidence intervals (CIs) will be reported. A test of hypothesis will be conducted using Pearson Chi-Square test at the 5% two-sided significance level to formally compare the treatment arms. The primary analysis will be performed in the CC analysis population and repeated as a secondary analysis in the ITT and PP analysis populations. Additional subgroup analyses may be performed and will be specified in the SAP.

Microbiologic cure will be determined from the rectal CT NAAT result. For the primary analysis, microbiologic cure at Visit 3 will be defined using the criteria in Table 2 below.

Table 2: Interpretation of Rectal CT NAAT Results for Day 29 Analyses

Visit 2 (Day 15) NAAT Result	Visit 3 (Day 29) NAAT Result	Clinical Interpretation at Visit 3 (Day 29)	Microbiologic Cure Status for Primary Analysis
Negative	Negative	Cure	Cure
Negative	Positive	Reinfection or Recrudescence	Failure
Negative	Unknown	Unknown	Unknown
Positive	Negative	Delayed RNA clearance	Cure

Positive	Positive	Failure	Failure
Positive	Unknown	Unknown	Unknown
Unknown	Negative	Cure or Delayed RNA clearance	Cure
Unknown	Positive	Reinfection or Recrudescence	Failure
Unknown	Unknown	Unknown	Unknown

For CC and PP analyses, subjects with Unknown microbiologic cure status will be excluded. For ITT analyses, such subjects will be included with their cure status imputed. Secondary and sensitivity analyses that explore different methods for assessing the effect on Day 29 analyses of missing data, possible reinfections, behavioral and sexual data, and partner treatment completion will be performed. Details of these analyses will be specified in the SAP.

Microbiologic cure status for Day 15 analyses will be defined similarly; details will be specified in the SAP.

10.4.4.2 Secondary Efficacy Analysis

To compare the efficacy of azithromycin vs. doxycycline for treatment of rectal CT according to LGV subgroup (a binary classification), the number and proportion of subjects with microbiologic cure at Visit 3 will be summarized in each subgroup overall and by treatment. The point estimates for the treatment-specific proportions and difference in proportions as well as corresponding 95% CIs will be reported within each subgroup.

To compare the efficacy of azithromycin vs. doxycycline for treatment of rectal CT at Visit 2, the number and proportion of subjects with microbiologic cure at Visit 2 will be summarized in each subgroup overall and by treatment. The point estimates for the treatment-specific proportions and difference in proportions as well as corresponding 95% CIs will be reported within each subgroup.

All secondary efficacy analyses will be performed in the ITT, CC, and PP analysis populations. Any additional subgroup analyses will be specified in the SAP.

10.4.4.3 Exploratory Efficacy Analysis

Details of the exploratory efficacy analysis, as well as any additional exploratory analyses that may be performed to supplement the primary and secondary analyses, will be described in the SAP.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each site will maintain appropriate medical and research records for this trial, 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 study records for the purposes of quality assurance (QA) reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, 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 the pharmacies, laboratories, and medico-technical departments involved in the trial. Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

12 QUALITY CONTROL AND QUALITY ASSURANCE

Following a written DMID-accepted site quality management plan, the site is responsible for conducting routine QA and quality control (QC) activities to internally monitor study progress and protocol compliance. The site PI will provide direct access to all trial-related sites, source documents, DCFs, and reports for inspection by the sponsor and/or local and regulatory authorities. The site PI will ensure all study personnel are appropriately trained and applicable documentations are maintained on site.

The SDCC will implement QC procedures beginning with the IDES and generate data QC checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification and resolution.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 Ethical Standard

The site PI will ensure that this trial is conducted in full conformity with principles of the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the 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 56, and ICH E6; 62 Federal Regulations 25691 (1997), if applicable. The site PI's institution will hold a current Federal Wide Assurance (FWA) issued by the Office of Human Research Protection (OHRP) for federally funded research.

13.2 Institutional Review Board

Before enrollment of subjects into the trial, the approved protocol and ICF will be reviewed and approved by the appropriate IRB listed on its FWA.

The responsible official for the IRB will sign the IRB letter of approval of the protocol before the start of the trial and provide a copy to DMID. The IRB's FWA number will be provided to DMID.

Should amendments to the protocol be required, they will be written by the sponsor and provided to the site PI for submission to the IRB.

13.3 Informed Consent Process

The site PI, or designated study staff, will choose subjects in accordance with the eligibility criteria detailed in Section 5. Before any study procedures are performed, subjects must sign an ICF that complies with the requirements of 21 CFR Part 50, 45 CFR Part 46, and the local IRB.

Informed consent is a process that is initiated before an individual agrees to participate in a trial and continues throughout the subject's trial participation. The informed consent documentation may be separate forms or combined into a single form with two parts according to local IRB requirements as follows:

1. The Screening Informed Consent (SIC) for consent to defer presumptive empiric treatment and abstain from sex of any kind (oral, anal, or vaginal) until CT and GC NAAT results are available. This is applicable to potential subjects defined as high risk (i.e., who meet either of the following criterion: a) known contact to chlamydia and report receptive anal intercourse in the past 30 days or b) clinician assessment that empiric treatment is indicated).

2. The Screening and Enrollment Informed Consent is for participation in the full study.

Before any study procedures are performed, subjects will receive a comprehensive explanation of the proposed study procedures and study interventions/products, including the nature and risks of the trial, alternate therapies, any known adverse events (AEs), the approved status of the components, and the other elements that are part of obtaining proper informed consent. Subjects will also receive a detailed explanation of the proposed use and disclosure of their protected health information, including specifically their specimens. Subjects will be allowed sufficient time to consider participation in the trial and, after having the nature and risks of the trial explained to them, will have the opportunity to discuss the trial with their family, friends, or legally authorized representative, or think about it before agreeing to participate.

Depending whether the subject has a confirmed/unconfirmed diagnosis of rectal CT, they will be given the appropriate form of the ICF describing in detail the study interventions/products, study procedures, risks, and possible benefits. The ICF must not include any exculpatory statements. ICF will be IRB-approved, and subjects will be asked to read and review the appropriate document. Upon reviewing the appropriate document, the site PI (or designee) will explain the research study to subjects and answer any questions that may arise. Subjects must sign the ICF before starting any study procedures/interventions being done specifically for the trial, including administering study drug.

DMID will provide the site PI, in writing, any new information that significantly affects the subjects' risk of receiving the study drug. This new information will be communicated by the site PI to subjects who consent to participate in the trial in accordance with IRB requirements. The ICF will be updated, and subjects will be re-consented per IRB requirements, if necessary.

Study personnel may employ IRB-approved recruitment efforts before obtaining the subject's consent; however, before any study procedures are performed to determine protocol eligibility, an ICF must be signed. Subjects will be given a copy of the ICF(s) that they sign.

By signing the SIC (if applicable) and Screening and Enrollment ICF, subjects agree to complete all evaluations required by the trial, unless the subject withdraws voluntarily or is terminated from the trial for any reason.

The rights and welfare of subjects will be protected by emphasizing to subjects that the quality of their medical care will not be adversely affected if they decline to participate in or withdraw from this trial.

13.4 Exclusion of Women, Minorities, and Children (Special Populations)

The study population in this trial will include male adults (defined as male sex at birth) who meet the subject inclusion/exclusion criteria, regardless of religion, race, or ethnic background. STD treatment guidelines recommend routine screening for rectal chlamydia in MSM. Routine screening in women and men who have sex with women only is not recommended or routinely done in practice. Therefore, the study will exclude women and children. Should the outcome of this trial be deemed acceptable, additional trials may be initiated in other populations.

13.5 Subject Confidentiality

Subjects will have code numbers and will not be identified by name. Subject confidentiality is strictly held in trust by the site PIs, their study personnel, the sponsor(s), and their agents. This confidentiality is extended to cover testing of biological samples, in addition to the clinical information relating to subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the trial or data from the trial will be released to any unauthorized third party without prior written approval of the sponsor.

All information provided by the sponsor and all data and information generated by the site as part of the trial (other than a subject's medical records) will be kept confidential by the site PI and other study personnel to the extent permitted by law. This information and data will not be used by the site PI or other study personnel for any purpose other than conducting the trial. These restrictions do not apply to: (1) information that becomes publicly available through no fault of the site PI or other study personnel; (2) information that is necessary to disclose in confidence to an IRB solely for the evaluation of the trial; (3) information that is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results that may be published as described in Section 16. If a written contract for the conduct of the trial that includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

Applicable regulatory authorities, such as the FDA, other authorized representatives of the sponsor, or the local IRB/IEC may inspect all documents and records required to be maintained by the site PI. This includes, but is not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this trial. The sites will permit access to such records.

To protect privacy, a Certificate of Confidentiality (CoC) has been obtained. With this CoC, 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 CoC to resist any demands for information that would identify the subject, except as explained below.

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

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

The CoC 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.

13.6 Study Discontinuation

If the trial is discontinued, subjects who signed the Screening and Enrollment ICF and were randomized and treated will continue to be followed for safety assessments. No further study drug will be administered.

13.7 Future Use of Stored Specimens

Before any testing is done on stored samples, the tests must be reviewed and approved by DMID and the local IRB/IEC of the researcher requesting the specimens.

13.7.1 Specimens Collected for Study Testing

Laboratory evaluations using the Aptima Combo 2® NAAT for CT and PCR assay for LGV will be conducted at the UW Global Health STI Laboratory. Specimens may be needed for further testing in the context of this trial. Archived specimens will be identified only by the specimen number, which will allow linkage of the samples to study data but not to any personal identifiers. A subject's specimen will be kept until it is used up or destroyed the end of this trial.

If the subject consents, the remaining specimen may be stored and be kept indefinitely at UW for future testing in research related to rectal infections. If a subject decides at any time to not want the sample stored for future research, the subject must contact the nurse/clinician who will then notify the laboratory/specimen archive. The laboratory staff will then mark the swab samples with a "Destroy" label and destroy them at the end of this trial, or laboratory staff will remove the samples from storage and destroy them as soon as possible.

13.7.2 Additional Specimens Collected for Possible Future Testing

Permission will be sought from each subject to collect two additional rectal swabs for storage and possible future testing in research related to rectal infections. Subjects do not need to agree to collection of additional swabs for storage and future testing, and they may choose only to participate in the trial. Should the subject choose not to consent to collection of future use storage swabs, their medical care will not be impacted by this decision.

If the subject does consent to collection of additional swabs for storage and future use, the specimens will be kept until they are used for research purposes or stored indefinitely at the University of Washington. The swab containers will only be labeled with a specimen number linked to the subject number assigned at the clinic where the subject is enrolled. If a subject decides at any time after providing consent to not want the specimen stored for future research, the subject must contact the local site nurse/clinician, who will then notify the laboratory or specimen archive to destroy the specimens.

There will be no direct benefit to the subject from allowing the specimen to be stored and used for future purposes. However, the results may provide information that will help in the diagnosis or treatment of future patients.

14 DATA HANDLING AND RECORD KEEPING

The site PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

DCFs will be derived from the eCRF and provided by the SDCC to record and maintain data for each subject enrolled in the trial. All DCFs should be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue ink is required to ensure clarity of reproduced copies. When making a change or correction, 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.

Data reported in the eCRF derived from the DCFs should be consistent with the DCFs, or the discrepancies should be explained.

The sponsor and/or its designee will provide guidance to site PIs and other study personnel on making corrections to the DCFs and eCRFs.

14.1 Data Management Responsibilities

All DCFs must be reviewed by the clinical team and data entry personnel, who will ensure that they are accurate and complete. SAEs must be assessed for severity and relationship and reviewed by the site PI or appropriate sub-investigator.

Data collection is the responsibility of the study personnel at the sites under the supervision of the respective site PI. During the trial, the site PI must maintain complete and accurate documentation for the trial.

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

14.2 Data Capture Methods

Clinical data (including, but not limited to, SAEs, concomitant medications, and physical assessments) will be entered into a 21 CFR 11-compliant IDES, Advantage eClinical®, provided by the SDCC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the DCFs completed by the study personnel.

14.3 Types of Data

Data for this trial will include safety, laboratory, and outcome measures.

14.4 Timing/Reports

Interim and final reports of efficacy and SAEs will be prepared following the availability of all relevant data.

14.5 Study Records Retention

Records and documents pertaining to the conduct of this trial, including DCFs, source documents, ICFs, laboratory test results, and study drug inventory records, must be retained by the investigator for at least 2 years following the completion of this trial. No records may be destroyed without written permission from the sponsor.

14.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or protocol-specific MOP requirements. Noncompliance may be either on the part of the subject, the site PI, or the study site staff. As a result of 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 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 must be promptly reported to DMID, via the SDCC's Advantage eClinical®.

All protocol deviations, as defined above, must be addressed in study subject DCFs. A completed copy of the DMID Protocol Deviation Form must be maintained in the regulatory file, as well as in the subject's study chart. Protocol deviations must be sent to the local IRB per their guidelines. The site PI and other study personnel are responsible for knowing and adhering to their IRB requirements.

15 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 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 the 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 this protocol (and its amendments) and a copy of the SAP will be posted on ClincialTrials.gov.

For this trial, 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

16 LITERATURE REFERENCES

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APPENDIX A: SCHEDULE OF EVENTS

Procedures	Visit 0, Day -30 to -1 (Screening)[14]	Visit 1, Day 1 (Screening/ Baseline)	Visit 2, Day 15 (Day 12-18)	Visit 3, Day 29 (Day 25-31)	Unscheduled Visit[15]
Informed Consent[1]	X	X			
Demographics	X	X			
Review Inclusion/Exclusion Criteria	X[16]	X			
Confirmation of Positive CT NAAT[2]		X			
HIV Testing and Treatment History[3]		X	X	X	X
Sexual and STD History[4]		X	X	X	X
Prior and Concomitant Medications[5]		X	X	X	X
Symptom Review[6]		X	X	X	X
Targeted Physical Examination[7]		X	X	X	X
Rectal Swab Collection for CT NAAT, Future Use[8]		X	X	X	X
Randomization		X			
Study Drug Dispensation, Dosing Instructions, and First Dose Taken in Clinic		X			
Review Protocol Requirements[9]		X	X		X
Contact Information[10]	X	X	X		X
Study Drug Vial Collection			X	X[12]	X[13]
Assess Adherence[11]		X	X	X[12]	X[13]
Serious Adverse Events			X	X	X

1 Potential participants identified as high risk will be asked to consent to defer empiric treatment and abstain from sex until NAAT results are available. Upon receipt and confirmation of a positive CT and negative GC result, they will need to consent to participate in the full study prior to continuation.

2 Confirm untreated rectal CT diagnosed with a positive NAAT result obtained via laboratory report or EMR printout.

3 At baseline, collect HIV testing and treatment history by interview of subject; at follow-up visits, review HIV testing and treatment history and update as appropriate.

4 At baseline, collect sexual and STD history for the past 60 days; at follow-up visits, collect interim sexual and STD history since the last visit.

5 At baseline, record all prior medications taken in the last 21 days before initiating study drug; at follow-up visits, record any concomitant medications taken since the last study visit and update prior medications, as appropriate.

6 The presence or absence of individual rectal symptoms and inguinal lymphadenopathy will be obtained by interview of the subjects and documented. The investigator will state whether the rectal sign or symptom reported by the subject is related to rectal CT and indicate if the subject was symptomatic or asymptomatic for the reported rectal sign or symptom.

7 At baseline, examine the inguinal lymph nodes and, if indicated based on subject report of symptoms, a more extensive physical exam of the genitals and anorectum will be performed. For subjects who complete follow-up in the clinic, a targeted physical examination (genitals, inguinal lymph nodes, and anorectum) will be performed if applicable based on subject-reported symptoms,

8 Obtain one rectal swab from all subjects for CT testing (clinician- or self-collected). Collect two additional rectal swabs for storage and future use from consenting subjects who present to the clinic for study visits.

9 At baseline, review study protocol requirements with the subject; at follow-up visits, remind the subject to abstain from receptive anal sex or use condoms during receptive anal sex for the duration of the trial.

10 At screening and baseline, collect subject information for follow-up and study visit reminders; at follow-up visits, review and update contact information accordingly.

[11] At Visit 1, adherence to azithromycin (or placebo) plus one doxycycline capsule (or placebo) will be observed by clinic staff. At Visit 2 (or the appropriate follow-up visit if Visit 2 was missed or the assessment was not conducted), adherence to doxycycline (or placebo) will be assessed by subject interview. For subjects who return to clinic for follow-up visits, study drug vials will be collected (if returned) and the number of remaining pills counted (if any) will be counted.

[12] If not already done at Visit 2 (or at an Unscheduled Visit if Visit 2 was missed or the assessment was not conducted).

[13] If after the dosing period is complete and adherence has not yet been assessed, study drug vial collection and subject interview are at the discretion of the site PI.

[14] Only applicable to potential subjects identified as high risk who do not have a confirmed diagnosis for rectal CT.

[15] At Unscheduled Visits, procedures are performed at the discretion of the site PI.

[16] A subset of criteria will be assessed at Visit 0.