CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN

for

DMID Protocol: 17-0092

Study 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

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STUDY TITLE

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Form/Route:	Orally
Indication Studied:	Rectal Chlamydia
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
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This study was performed in compliance with Good Clinical Practice.

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LIST OF ABBREVIATIONS

AE	Adverse Event
CC	Complete Case
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CT	*Chlamydia trachomatis*
CRF	Case Report Form
DCF	Data Collection Form
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GC	*N. gonorrhoeae*
GI	Gastrointestinal
HIV	Human Immunodeficiency Virus
HMC	Harborview Medical Center
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDES	Internet Data Entry System
IDS	Investigational Drug Services
IRB	Institutional Review Board
ITT	Intention-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
NIH	National Institutes of Health
OTC	Over-the-Counter
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PP	Per Protocol

List of Abbreviations *(continued)*

PrEP	Pre-exposure prophylaxis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
STD	Sexually Transmitted Disease
STI	Sexually Transmitted Infection
US	United States
UW	University of Washington
WHO	World Health Organization

1. PREFACE

The Statistical Analysis Plan (SAP) for "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 17-0092) describes and expands upon the statistical information presented in the protocol.

This document describes all planned analyses and provides reasons and justifications for these analyses. It also includes sample tables, listings, and figures planned for the interim analyses and final analyses. Regarding the interim analyses, the final analyses and manuscript, this SAP follows the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines and is consistent with Topic E8 (General Considerations for Clinical Trials) and Topic E9 (Statistical Principles for Clinical Trials). The structure and content of the SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA) and ICH, while all work planned and reported for this SAP will follow internationally accepted guidelines published by the American Statistical Association and the Royal Statistical Society for statistical practice.

This document contains four sections: (1) a review of the study design, (2) general statistical considerations, (3) comprehensive statistical analysis methods for efficacy and safety outcomes, and (4) a list of proposed tables, listings and figures. Any deviation from this SAP will be described and justified in protocol amendments and/or the manuscript, as appropriate. The reader of this SAP is encouraged to also review the study protocol for details on conduct of the study and the operational aspects of clinical assessments.

2. INTRODUCTION

2.1. Study Background

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 [reference 1 in the protocol], 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 [references 2-5 in the protocol].

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 [reference 6 in the protocol]. 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.

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 [reference 7 in the protocol]. 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[reference 8 in the protocol]. 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[reference 9 in the protocol]. 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.

2.2. Purpose of the Analyses

These analyses will assess the efficacy and safety of azithromycin 1-gram single dose or doxycycline 100 mg twice daily for 7 days for the treatment of rectal CT in MSM and will be included in the final manuscript.

3. STUDY OBJECTIVES AND ENDPOINTS

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

1 To assess the effect of LGV infection on microbiologic cure in MSM with rectal CT at Days 15 and 29.

2 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. Endpoints

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

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

2 The proportion of subjects with microbiologic cure in each study arm at Day 15.

3.2.3. Exploratory Outcome Measures

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.

3.3. Study Definitions and Derived Variables

3.3.1. Microbiologic Cure Status at Visit 3

Microbiologic cure will be based on rectal CT NAAT results. For the primary analysis, microbiologic cure at Visit 3 (Day 29) will be defined using the criteria in Table 1 below.

Table 1: 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

Subjects will be classified as non-evaluable if they:

- did not return for Visit 3, or
- their NAAT results at Visit 3 were not available for any reason, or
- they could not be evaluated for microbiological outcome status at Visit 3 for any other reason.

3.3.2. Microbiologic Cure Status at Visit 2

Microbiologic cure status at Visit 2 (Day 15) will be defined using the criteria in Table 2 below.

Table 2: Interpretation of Rectal CT NAAT Results for Day 15 Analyses

Visit 2 (Day 15) NAAT Result	Clinical Interpretation at Visit 2 (Day 15)	Microbiologic Cure Status for Secondary Analysis
Negative	Cure	Cure
Positive	Failure	Failure
Unknown	Unknown	Unknown

Subjects will be classified as non-evaluable if they:

- did not return for Visit 2, or
- their NAAT results at Visit 2 were not available for any reason, or
- they could not be evaluated for microbiological outcome status at Visit 2 for any other reason.

3.3.3. Within Window Test of Cure Visit

Test of Cure Visit 2 will be considered within window if the visit occurred between Days 12 and 18 (inclusive) after the first dose of study drug.

Test of Cure Visit 3 will be considered within window if the visit occurred between Days 25 and 31 (inclusive) after the first dose of study drug.

3.3.4. Treatment Adherence

Subjects will be considered sufficiently adherent with study treatment if they take the initial dose of azithromycin (or placebo) and initial dose of doxycycline (or placebo) and at least 9 additional doses of doxycycline (or placebo) within 10 days (inclusive) of the completed initial dose.

An alternative definition of sufficiently adherent will also be explored. Subjects will be considered sufficiently adherent under this alternate definition if they:

- take the initial dose of azithromycin (or placebo) and initial dose of doxycycline (or placebo), and
- take at least 80% of the scheduled doses of doxycycline capsule (or placebo) (i.e., at least 12 of the 14 doses) as assessed by the subject-reported number of missed doses within in 7 days (inclusive) of the completed initial dose.

3.3.5. Initial Completed Dose and Timing of Subsequent Doses

Subjects will be considered to have taken the initial dose of azithromycin (or placebo) and initial dose of doxycycline (or placebo) in the clinic if they are observed to take the doses and do not report vomiting within two hours of administration.

If a subject vomits, he is able to return to the study clinic for retreatment within 48 hours. If he returns within 48 hours and is able to swallow the doses and not vomit within two hours of administration, he will be considered to have taken the initial dose of azithromycin (or placebo) and initial dose of doxycycline (or placebo).

For subjects who take the initial dose and do not report vomiting, the timing requirements for sufficiently adherent determination described in Section 3.3.4 (i.e. within 10/7 days of completed initial dose) will be with respect to the initial study clinic visit date. For subjects who take the retreatment dose, the timing requirements will be with respect to the retreatment visit date for azithromycin (or placebo) and for the earliest completed dose of doxycycline (or placebo) as applicable (e.g., at the retreatment visit or in the interim following the vomited dose, prior to the retreatment visit).

3.3.6. Baseline Value

The baseline value will be defined as the last value obtained prior to the first dose of study products.

3.3.7. LGV Infection Status

The LGV infections status is determined by the laboratory multiplex polymerase chain reaction (PCR) test. If LGV strains of CT are detected at baseline, the subject's LGV infection status will be classified as positive. Otherwise, the subject will be classified as negative.

3.3.8. HIV Status

Baseline HIV status will be based on subject report at the enrollment visit. 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. For subjects who are tested at baseline, their baseline HIV status will be based on the results of the testing.

At each follow-up visit, any changes to the subject's HIV status will be documented.

3.3.9. Antacid Use Status

Antacid use will be assessed at baseline, Visit 2, and Visit 3. Subjects who report use of antacids at baseline or follow-up visits as documented on the Visit Documentation form will be classified as using antacids. Subjects who do not report antacid use at all study visits will be classified as not using antacids.

3.3.10. Symptomatic/Asymptomatic Status

Rectal symptoms and inguinal lymphadenopathy will be assessed at baseline, Visit 2, and Visit 3. Based on these assessments, the investigator will document whether the rectal symptoms reported by the subject are related to rectal CT and will indicate if the subject is symptomatic or asymptomatic for rectal CT if a rectal sign or symptom was reported. This indication at baseline will determine each subject's baseline symptomatic status.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 4, 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 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.

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 are 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 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). Subjects who consent to collection and storage of swabs for future use have two additional swabs collected by the clinician (one for storage in culture media and one frozen). All subjects are 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 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 are 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 is 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 follow-up visits. At Visits 2 and 3, subjects are 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 have one rectal swab collected (clinician- or self-collected according to the subject's preference) for CT and LGV testing (NAAT). Subjects who consent to collection and storage of swabs for future use and return to the clinic for follow-up visits have two additional swabs collected by the clinician (one for storage in culture media and one

frozen) at each follow-up visit. Subjects who choose to self-collect rectal NAAT swabs outside the clinic 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) are contacted and referred to a care provider in the general clinic for appropriate treatment. At that appointment, those subjects learn which treatment they received during the trial.

A Data and Safety Monitoring Board (DSMB) will review a formal analysis of efficacy and SAEs when approximately half (N=123) of subjects have contributed primary outcome measure data, and at a final closeout meeting, held at the end of the trial after the database is locked and when the final study report is available. The DSMB may also meet at other specified times (as defined in the DSMB Charter) to assess operational characteristics of the trial.

Figure 1 presents the schematic of the study design and Table 4 presents the schedule of events.

4.2. Discussion of Study Design, Including the Choice of Control Groups

It is hypothesized that doxycycline will be more effective than azithromycin in achieving microbiologic cure of rectal CT, however to date, only non-randomized retrospective studies have compared the effectiveness of doxycycline and azithromycin for the treatment of rectal CT. Thus, a placebo-blinded, randomized controlled trial is necessary to definitively compare the clinical efficacy of doxycycline and azithromycin. This trial aims to meet this need.

4.3. Selection of Study Population

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.

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

4.4. Treatments

4.4.1. Treatments Administered

Subjects are randomized to receive one of two active treatments: azithromycin 250 mg × 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 dates of the first treatment will be by site in Table 5 and treatment group in Table 6.

4.4.2. Identity of Investigational Product(s)

Active Azithromycin

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

Placebo Azithromycin

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

Active Doxycycline

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

Placebo Doxycycline

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

4.4.3. Method of Assigning Subjects to Treatment Groups (Randomization)

Subjects will be randomized 1:1 to receive doxycycline or azithromycin. The trial will use a site-stratified, permuted, blocked randomization scheme.

The list of randomized treatment assignments is included in the enrollment module of Emmes' 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 has 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 is distributed to the subject.

4.4.4. Selection of Doses in the Study

Subjects are randomized to one of two treatment assignments:

- Azithromycin 250 mg × 4 (1 gram) orally as a single dose plus placebo doxycycline × 1 orally twice daily for 7 days (14 capsules total).
- Doxycycline 100 mg × 1 orally twice daily for 7 days (14 capsules total) plus placebo azithromycin × 4 orally as a single dose

The selected doses are consistent with the 2015 CDC Sexually Transmitted Disease Treatment Guidelines for CT infection.

4.4.5. Selection and Timing of Dose for Each Subject

Study staff 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 provide instructions for continued twice-daily doxycycline (or placebo) for 7 days to complete 14 doses. Subjects are asked to bring the vial of doxycycline (or placebo) back to the clinic at Visit 2. The dosing regimens are consistent with the 2015 CDC Sexually Transmitted Disease Treatment Guidelines for CT infection.

A subject who vomits the first dose of azithromycin (or placebo) and one doxycycline capsule (or placebo) within 2 hours of ingestion is 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 is 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 is asked to return to clinic as soon as possible to receive replacement study drug. At that time, the study clinician or designee provides 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 are asked to bring the vial of doxycycline (or placebo) back to the clinic at Visit 2.

4.4.6. Blinding

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 are blinded to treatment assignment. The DSMB may 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 is prepared at the UW Harborview Medical Center (HMC) Investigational Drug Services (IDS) in numbered, placebo-controlled kits. All kits look identical and contain an identical number of pills. Emmes provides 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 has access to an unblinded treatment report that indicates the actual treatment received, which is disclosed to the subject at an appointment with a care provider in the general clinic.

4.4.7. Prior and Concomitant Therapy

Administration of any medications will be recorded on the appropriate DCF. Concomitant medications 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) is included, as well as, herbs, vitamins, and other supplements. Previously recorded medications are updated as appropriate.

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

4.4.8. Treatment Adherence

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 is recorded on the appropriate data collection form (DCF). Subjects who voluntarily discontinue study drug before completing the dosing regimen remain in the trial and are followed for safety and efficacy. See Section 3.3.4 for the definition of adherence to treatment.

4.4.9. Efficacy and Safety Variables

For safety and efficacy analyses, multiple observations within a specific visit period are accepted. In the case of multiple observations within a specific window, the assessment value that is closest to the scheduled visit window will be used in the analyses for the post-baseline records. If observations have the same distance to the scheduled assessment, the latest one will be used. For screening and baseline visits, the last assessment value will be used. All the recorded data will be listed.

Efficacy Variables

See Section 3.3 for efficacy variable definitions. Microbiologic cure is the efficacy variable utilized in primary and secondary analyses.

Safety Variables

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.

Serious Adverse Event

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*,

  *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.
- 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.

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.

5. SAMPLE SIZE CONSIDERATIONS

The sample size and power calculations were derived 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. 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 [reference 10-13 in protocol], 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 [reference 14-20 in protocol]. 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 [reference 9 in protocol]. See Table 3 below for power estimates.

Table 3: 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% [reference 21, 22 in protocol].

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

Tabulations will be used extensively to summarize the data. All continuous variables will be summarized using the following descriptive statistics: n (sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the sample size) of observed levels will be reported for all categorical measures. Wilson confidence intervals for binomial proportions and difference in binomial proportions will be computed for efficacy variables. For the hypothesis tests comparing treatment groups with respect to efficacy outcomes, the two-sided Pearson Chi-Square test will be used. A 5% two-sided significance level will be used; i.e. two-sided 95% confidence intervals will be generated.

All summary tables will be structured with a column/sub-table for each treatment group (Azithromycin, Doxycycline, and All Subjects). In general, all data will be summarized by treatment group and/or site, and when appropriate by visit number. The total population size relevant to that table/column if applicable, including any missing observations will be displayed in the tables.

Data listings will be provided for all data. Note that in the data listings, Subject ID is the unique subject identifier, not the Study ID used on study and dates will not be included, only Study Day.

6.1.1. Pseudo Code

The following SAS® pseudo code will be used to calculate the following:

Chi-Square test at 5% two-sided significance level and odds ratio (and 95% asymptotic CI):

```
proc freq;
      Table treatment*analysis_variable / chisq;
      ods output ChiSq=outputdsn1;
      ods output RelativeRisks=outputdsn2;
run;
```

Fisher's Exact test at 5% two-sided significance level:

```
proc freq;
      Table treatment*analysis_variable / exact;
      ods output FishersExact=outputdsn;
run;
```

95% Wilson CI for proportions/percentages:

```
proc freq;
      Table treatment*analysisvariable / binomial(wilson);
      ods output binomialcls=outputdsn;
run;
```

95% Wilson CI for difference in proportions (produces Newcombe CI):

```
proc freq;
      Table treatment*analysisvariable / riskdiff(cl=Wilson);
      Exact Riskdiff;
      ods output pdiffcls=outputdsn;
run;
```

6.2. Timing of Analyses

The interim analysis will be conducted when approximately half (n=123) of subjects have contributed primary outcome measure data.

The final analysis will be performed after database lock when all subjects have been followed through Visit 3, the final study visit, at Day 29 (Window: Day 25-31).

6.3. Analysis Populations

6.3.1. Safety Analyses

All Safety analyses will be performed in the safety analysis population. The safety population includes all randomized subjects who receive at least one dose of study drug.

6.3.2. Efficacy Analyses

6.3.2.1. Intent-to-Treat Analysis (ITT) Population

The Intent-to-Treat (ITT) population includes all randomized subjects, regardless of whether they received study treatment, had a positive baseline rectal CT NAAT result, or were compliant with the administration procedures or schedule.

6.3.2.2. Complete Case (CC) Population

The Complete Case (CC) 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, microbiological data must be available from the Day 29 visit.

The CC population will be the primary efficacy analyses population.

6.3.2.3. Per-Protocol (PP) Population

The Per-Protocol (PP) 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 assigned study drug regimen (defined in Section 3.3.4), and do not experience either 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):

- Receipt of 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.

6.3.2.4. Considerations for Analysis Populations

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.

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, treatment adherence, 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

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 treatment failures and reviewed by the blinded case committee for inclusion in PP analyses.

6.3.2.5. Analysis Population Summaries

Table 7 summarizes the Safety, CC and PP analysis population eligibilities by randomized treatment group and reasons excluded. Subjects will be included in the count for a particular reason for exclusion if they met that criterion. As subjects may meet more than one criterion for exclusion, the "Excluded from…" counts may be less than the sum of the individual reason counts. A subject listing of analysis population eligibilities and the reasons for exclusion will be provided (Listing 1). A listing of subjects whose assigned treatment group does not match their randomized treatment group will be provided in Listing 2.

6.4. Covariates and Subgroups

The protocol defines formal subgroup analyses as secondary and exploratory analyses, however the study is not powered to make definitive claims regarding any of the subgroup analyses. Subgroups defined by LGV infection at baseline, HIV status at baseline, adherence to study drug, antacid medication use, and symptomatic status will be analyzed separately. Analyses for each subgroup will include estimation of microbiologic cure rate, differences of rates, and their confidence intervals. See Section 8 for more details.

6.5. Missing Data

Subjects with unknown microbiologic cure status will be excluded from the CC and PP population. For ITT analyses, such subjects will be included with their cure status imputed as microbiological failures.

6.6. Interim Analyses and Data Monitoring

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. 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). Details of the analyses are provided in Section 8.

6.7. Multicenter Studies

Safety and efficacy data will be pooled across all clinical sites. Center effects are not anticipated because treatment is self-administered, the sites are using standardized procedures for assessment of serious adverse events, and the study relies on a central laboratory for NAATs and PCR testing. See Section 8 and Section 9 for more details.

6.8. Multiple Comparisons/Multiplicity

O'Brien-Fleming boundaries will be utilized for the interim and final analyses to account for the formal interim analysis while maintaining an overall Type I error rate of 5%. Section 8 for details.

7. STUDY SUBJECTS

7.1. Disposition of Subjects

Table 8 will present the number of subjects who failed screening and number of subjects that failed to meet each eligibility criterion. Table 9 will present the disposition of subjects overall and by randomized treatment group. A listing of subject who completed the study, terminated early from study, or discontinued treatment and the reason for early termination or treatment discontinuation will be included in Listing 3.

Figure 2 is a flowchart showing the disposition of study subjects in the safety and efficacy analyses, adapted from the CONSORT statement [1]. It shows the number of subjects eligible, enrolled and randomized, and analyzed for the safety and efficacy analyses, overall and by treatment group.

7.2. Protocol Deviations

A summary of subject-specific protocol deviations will be presented by the deviation category, the type of deviation, and randomized treatment group for all enrolled subjects (Table 10). All subject-specific protocol deviations and non-subject-specific protocol deviations will be individually listed, as well (Listing 4 and Listing 5, respectively).

8. EFFICACY EVALUATION

8.1. Interim Analysis

The primary efficacy endpoint for the interim analysis is the proportion of subjects with microbiologic cure in each study arm at Day 29. See Section 3.3.1 for the definition of microbiologic cure.

A test of hypothesis comparing the proportion of subjects with microbiologic cure at Visit 3 (Day 29) in each treatment group will be conducted in the CC population. The null hypothesis for the comparison is that there is no difference in proportions between treatment arms, with a two-sided alternative that considers the possibility of a difference in either direction. The test will be conducted using a Pearson Chi-Square test at the 5% two-sided significance level. The resulting test statistic will be compared to the O'Brien Fleming bound calculated in the study's sample size calculations. At the interim point the bound is |2.79651|, thus if the test statistic is either greater than 2.79651 (Group A cure rate is higher than Group B cure rate) or less than -2.79651 (Group B cure rate is higher than Group A cure rate, then the resulting action should be to stop the trial. Otherwise, the resulting action should be to continue on to the full sample size.

The proposed summaries to be generated for the interim analysis were approved by the DSMB at the organizational meeting on 30MAY2018 and they are copied in this SAP. The summaries will be semi-blinded, where the treatment group labels will be "Group A" and "Group B". Table 11 will summarize eligibilities for and reasons for exclusion from the CC population for all randomized subjects. Table 12 will present the microbiological cure rates with confidence intervals by treatment group. Also included is the test statistic and the O'Brien Fleming critical value.

8.2. Final Analysis

8.2.1. Primary Efficacy Analysis

The primary efficacy endpoint for the final analysis is the proportion of subjects with microbiologic cure in each study arm at Day 29. See Section 3.3.1 for the definition of microbiologic cure.

A test of hypothesis comparing the proportion of subject with microbiologic cure at Visit 3 (Day 29), will be conducted in the CC population. The null hypothesis for the comparison is that there is no difference in proportions between treatment arms, with a two-sided alternative that considers the possibility of a difference in either direction. The test will be conducted using a Pearson Chi-Square test at the 5% two-sided significance level. The number of subjects, the proportion of subjects with microbiologic cure, and the 95% Wilson confidence interval for the proportion of subjects with microbiologic cure will be presented overall and by treatment group. In addition, the difference in proportions between the Azithromycin group and the Doxycycline group and 95% Wilson confidence intervals will be presented.

The test statistic will be compared to the O'Brien Fleming bound calculated in the study's sample size calculations to determine significance. At the final analysis the bound is |1.97743|, thus if the test statistic is either greater than 1.97743 (doxycycline cure rate is higher than azithromycin cure rate) or less than -1.97743 (azithromycin cure rate is higher than doxycycline cure rate), then the resulting interpretation is that the cure rates are significantly different between arms. Otherwise, the resulting interpretation is that the cure rates are not significantly different between arms.

The above analyses, apart from the O'Brien Fleming bound comparisons will be repeated in the ITT and PP analysis populations.

See Table 13, Table 14, and Table 15. See Section 6.1 for pseudocode to fit the above analyses. Individual efficacy response data is presented in Listing 6.

8.2.2. Secondary Efficacy Analyses

The first secondary efficacy endpoint is the proportion of subjects with microbiologic cure in each study arm at Day 15. The number of subjects, the proportion of subjects with microbiologic cure at Visit 2 (Day 15) will be summarized overall and by treatment. The same analyses as described in the previous section will be performed for the Visit 2 (Day 15) outcome (excluding O'Brien Fleming bound comparisons). See Table 16, Table 17**,** and Table 18.

The second secondary efficacy endpoint is the proportion of subjects with microbiologic cure in each treatment arm at Days 15 and 29 within subgroups defined by LGV infection at baseline. The number of subjects, the proportion of subjects with microbiologic cure at Visit 2 (Day 15) and Visit 3 (Day 29) will be summarized in each subgroup overall and by treatment. The point estimates for treatment-specific proportions and difference in proportions as well as corresponding 95% Wilson confidence intervals will be present within each subgroup at Visit 2 (Day 15) and Visit 3 (Day 29) for each analysis population. See Table 19, Table 20, Table 21, Table 22, Table 23, and Table 24.

8.2.3. Exploratory Efficacy Analyses

The exploratory outcome measure is 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 (all defined in Section 3.3). For the HIV analyses, subjects who enrolled HIV negative but became HIV positive prior to their Day 29 visit will be included in the ITT analysis and excluded from CC and PP analyses.

The number of subjects, the proportion of subjects with microbiologic cure at Visit 3 (Day 29) will be summarized in each subgroup overall and by treatment. The point estimates for treatment-specific proportions and difference in proportions as well as corresponding 95% Wilson confidence intervals will be present within each subgroup at Visit 3 (Day 29) for each analysis population. Proposed summaries begin at Table 25 and end at Table 36.

9. SAFETY EVALUATION

9.1. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized for all enrolled subjects. Ethnicity and race will be summarized by site (Table 37) and by randomized treatment group (Table 38). Ethnicity is categorized as Hispanic or Latino, or Not Hispanic or Latino. Race is categorized as American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Black or African American, White, Multi-Racial, or Unknown. In accordance with NIH reporting policy, subjects may self-designate as belonging to more than one race (Multi-Racial) or may refuse to identify a race (Unknown), the latter reflected in the Case Report Form (CRF) as "No" to each racial option. In addition, symptomatic status and the assessment of inguinal lymphadenopathy will be summarized by randomized treatment group. Age will be summarized by site (Table 39) and by randomized treatment group (Table 40). Baseline and follow-up STD and sexual history will be summaries by randomized treatment group (Table 41 and Table 42).

Individual subject listings will be presented for all demographics as well as baseline LGV infection, HIV, symptomatic status, and inguinal lymphadenopathy status (Listing 7), baseline and follow-up STD history (Listing 8), and baseline and follow-up sexual history (Listing 9).

9.1.1. Prior and Concomitant Medications

The use of prior and concomitant medications taken during the study will be recorded on the Concomitant Medication CRF. Concomitant medications will be coded to the Anatomical Therapeutic Classification using the WHO Drug Dictionary. Individual subject listings will be generated for all concomitant medications (Listing 10). A summary of antiretroviral therapy among HIV positive subjects and PrEP use among HIV negative subjects at baseline and follow-up will be presented (Table 43).

9.2. Measurements of Treatment Adherence

See Section 3.3.4 and for the definition of adherence to treatment that will be used for efficacy analyses.

The number of subjects not compliant with study treatment will be presented by treatment group as part of the analysis population eligibility table (Table 7**)**. Individual subject listing will be presented for treatment adherence data (Listing 11).

9.3. Adverse Events

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 are collected. Drug intolerance related adverse effects are collected when subjects report nonadherence of study drug treatment.

9.3.1. Drug Intolerance

A summary of adverse effects related to drug intolerance will be presented by visits (Table 44). Individual subject listing will be presented for all adverse effects related to drug intolerance (Listing 12). A summary of study product vomiting and re-treatment will be presented by treatment group (Table 45).

9.4. Deaths, Serious Adverse Events and other Significant Adverse Events

A listing of deaths and serious adverse events will be presented, which will include, but not limited to, Subject ID, treatment group, Adverse Event Description, Study Day the Event became Serious, Reason Reported as

an SAE, Relationship to Treatment, Alternate Etiology if Not Related, Outcome, and Duration of Event in days (Table 46).

9.5. Clinical Laboratory Evaluations

No clinical laboratory evaluations are performed for safety.

9.6. Physical Evaluations

A targeted physical examination is performed at Visits 1, 2 and 3 (if indicated). The following body systems are subject to being assessed: Abdomen, Cardiovascular/heart, Extremities, General Appearance, Genitourinary, HEENT, Lymph nodes, Musculoskeletal, Neck, Neurological, Oral, Pulmonary/Chest, Rectal, and Skin. Individual subject listings will be provided for abnormal physical exam findings (Listing 13). Also see Section 9.1 for summaries of baseline symptomatic and inguinal lymphadenopathy statuses.

10. PHARMACOKINETICS

Not applicable for this study.

11. IMMUNOGENICITY

Not applicable for this study.

12. OTHER ANALYSES

There are no additional analyses planned for this study.

13. REPORTING CONVENTIONS

P-values ≥0.001 and ≤0.999 will be reported to three decimal places; p-values less than 0.001 will be reported as "<0.001"; p-values greater than 0.999 will be reported as ">0.999". The mean, median, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles other than the median will use the same number of decimal places as the original data. Proportions will be presented to two decimal places; values <0.01 will be presented as "<0.01". Percentages will be reported to the nearest whole number; values < 1% will be presented as "<1". Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to three significant figures.

14. TECHNICAL DETAILS

SAS version 9.4 or above will be used to generate all tables, figures and listings.

15. SUMMARY OF CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

The analyses described in this document are consistent with what was specified in the study protocol. The exclusionary criteria for the per protocol population were modified slightly from what is stated in the protocol.

16. REFERENCES

1. Drummond R. CONSORT Revised: Improving the Reporting of Randomized Clinical Trials. JAMA. 2001; 285(15):2006-2007.

17. LISTING OF TABLES, FIGURES, AND LISTINGS

Table, figure, and listing shells are presented in Appendices 1, 2, and 3, respectively.

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Table 4: Schedule of Study Procedures

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 subjects identified as high risk will be asked to consent to defer empiric treatment and abstain from sex until NAAT results are available using the Screening Consent. 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 if a rectal sign or symptom was reported.
[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.

Table 5: Dates of First Treatment by Site – Safety Population

[Note: Dates will be categorized by breaking the calendar year into quarters and will be sorted chronologically.]

Dates of Dosing	University of Washington (N=X)		Fenway Health (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%
Total (Entire period of enrollment)	x	x	x	x	x	x
DDMMMYYYY-DDMMMYYYY	x	x	x	x	x	x
DDMMMYYYY-DDMMMYYYY	x	x	x	x	x	x
DDMMMYYYY-DDMMMYYYY	x	x	x	x	x	x
DDMMMYYYY-DDMMMYYYY	x	x	x	x	x	x

Note: N=Number of subjects in the safety population in the specified site.

Table 6: Dates of First Treatment by Treatment Group – Safety Population

[Note: Dates will be categorized by breaking the calendar year into quarters and will be sorted chronologically.]

Dates of Dosing	Azithromycin (N=X)		Doxycycline (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%
Total (Entire period of enrollment)	x	x	x	x	x	x
DDMMMYYYY-DDMMMYYYY	x	x	x	x	x	x
DDMMMYYYY-DDMMMYYYY	x	x	x	x	x	x
DDMMMYYYY-DDMMMYYYY	x	x	x	x	x	x
DDMMMYYYY-DDMMMYYYY	x	x	x	x	x	x

Note: N=Number of subjects in the safety population randomized to the specified treatment group.

Table 7: Safety, Complete Case, and Per-Protocol Analysis Population Eligibilities by Treatment Group

Analysis Populations	Eligibility Category	Reason Subjects Excluded	Azithromycin (N=X)		Doxycycline (N=X)		All Subjects (N=X)	
			n	%	n	%	n	%
Safety Analysis Population	Eligible for Safety Population		x	x	x	x	x	x
	Excluded from Safety Population	Any Reason	x	x	x	x	x	x
		Did not receive study product	x	x	x	x	x	x
Complete Case (CC) Analysis Population	Eligible for CC Population		x	x	x	x	x	x
	Excluded from CC Population	Any reason	x	x	x	x	x	x
		Did not meet all inclusion/exclusion criteria	x	x	x	x	x	x
		Did not have a positive baseline rectal CT NAAT result	x	x	x	x	x	x
		Post-baseline microbiologic data not available at Visit 2 (Day 15)	x	x	x	x	x	x
		Post-baseline microbiologic data not available at Visit 3 (Day 29)	x	x	x	x	x	x
Per-Protocol (PP) Analysis Population	Eligible for PP Population		x	x	x	x	x	x
	Excluded from PP Population	Any reason	x	x	x	x	x	x
		Did not meet all inclusion/exclusion criteria	x	x	x	x	x	x
		Did not have a positive baseline rectal CT NAAT result	x	x	x	x	x	x
		Post-baseline microbiologic data not available at Visit 2 (Day 15)	x	x	x	x	x	x
		Post-baseline microbiologic data not available at Visit 3 (Day 29)	x	x	x	x	x	x
		Received treatment for a symptomatic STD other than CT	x	x	x	x	x	x
		Exposed to an STD	x	x	x	x	x	x
		Received treatment with an antibiotic active against CT	x	x	x	x	x	x
		Had condomless receptive anal sex	x	x	x	x	x	x
		Did not sufficiently adhere to study drug	x	x	x	x	x	x

Note: N=Number of enrolled subjects randomized to the specified treatment group.

Table 8: Ineligibility Summary of Screen Failures

Category	Inclusion/Exclusion Criterion	n[a]	%[b]
Screen Failures	Number of screen failures	x	100
	Number of subjects failing any eligibility criterion	x	x
	Number of subjects declining enrollment	x	x
Failed Inclusion	Any inclusion criterion	x	x
	[inclusion criterion 1]	x	x
	[inclusion criterion 2]	x	x
	[inclusion criterion 3]	x	x
Failed Exclusion	Any exclusion criterion	x	x
	[exclusion criterion 1]	x	x
	[exclusion criterion 2]	x	x
	[exclusion criterion 3]	x	x
Declined Enrollment	Time commitment	x	x
	Concern of potential risks	x	x
	Number of procedures	x	x
	Unable to contact subject	x	x
	Other	x	x

[a] More than one criterion may be marked per subject.
[b] Denominator for percentages is the total number of screen failures.

Table 9: Subject Disposition by Treatment Group

Subject Disposition	Azithromycin (N=X)		Doxycycline (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%
Screened	--	--	--	--	x	--
Enrolled/Randomized	x	100	x	100	x	100
Received the First Dose of Treatment	x	x	x	x	x	x
Received All Scheduled Treatments[a]	x	x	x	x	x	x
Completed Follow-up (Study Day 29)[a]	x	x	x	x	x	x
Complied with Treatment[b]	x	x	x	x	x	x
Complied with Treatment by Alternative Definition of Treatment Adherence[b]	x	x	x	x	x	x

Note: N= Number of enrolled subjects randomized to the specified treatment group.
[a] Refer to Listing 3 for reasons subjects discontinued or terminated early.
[b] Refer to Section 3.3.4 for treatment adherence

Table 10: Distribution of Protocol Deviations by Category, Type, and Treatment Group

Category	Deviation Type	Azithromycin (N=X)			Doxycycline (N=X)			All Subjects (N=X)		
		# of Subj.	%	# of Dev.	# of Subj.	%	# of Dev.	# of Subj.	%	# of Dev.
Eligibility/enrollment	Any type	x	x	x	x	x	x	x	x	x
	Did not meet inclusion criterion	x	x	x	x	x	x	x	x	x
	Met exclusion criterion	x	x	x	x	x	x	x	x	x
	ICF not signed prior to study procedures	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x
Treatment administration schedule	Any type	x	x	x	x	x	x	x	x	x
	Out of window visit	x	x	x	x	x	x	x	x	x
	Missed visit/visit not conducted	x	x	x	x	x	x	x	x	x
	Missed treatment administration	x	x	x	x	x	x	x	x	x
	Delayed treatment administration	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x
Follow-up visit schedule	Any type	x	x	x	x	x	x	x	x	x
	Out of window visit	x	x	x	x	x	x	x	x	x
	Missed visit/visit not conducted	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x
Protocol procedure/assessment	Any type	x	x	x	x	x	x	x	x	x
	Incorrect version of ICF signed	x	x	x	x	x	x	x	x	x
	Specimen not collected	x	x	x	x	x	x	x	x	x
	Specimen result not obtained	x	x	x	x	x	x	x	x	x
	Required procedure not conducted	x	x	x	x	x	x	x	x	x
	Required procedure done incorrectly	x	x	x	x	x	x	x	x	x
	Study product temperature excursion	x	x	x	x	x	x	x	x	x
	Specimen temperature excursion	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x
Treatment administration	Any type	x	x	x	x	x	x	x	x	x
	Required procedure done incorrectly	x	x	x	x	x	x	x	x	x
	Study product temperature excursion	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x
Blinding policy/procedure	Any type	x	x	x	x	x	x	x	x	x
	Treatment unblinded	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x

Note: N=Number of enrolled subjects randomized to the specified treatment group.

Table 11: Interim Analysis CC Population Eligibility – All Enrolled Subjects

	Reason Subjects Excluded	Group A (N=X)		Group B (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Eligible for CC Analysis Population		x	x	x	x	x	x
Excluded from CC Analysis Population	Any Reason	x	x	x	x	x	x
	Reason 1	x	x	x	x	x	x
	Reason 2	x	x	x	x	x	x
	…	x	x	x	x	x	x

Notes: Denominator for percentages is the number of subjects enrolled (N) in the study randomized to the specified treatment group.
Subjects will be counted for a particular reason for exclusion if they met the criterion. As subjects may meet more than one criterion, the sum of the individual reasons may add up to more than the subjects excluded.

Table 12: Interim Analysis Microbiological Cure Rates – CC Population

Treatment Group	Number of Subjects	Number of Subjects with Microbiologic Cure	Interim Microbiologic Cure Proportion	Interim Confidence Interval	Test Statistic	Critical Value
Group A	x	x	0.xx	0.xx, 0.xx	x.x	+/- 2.79651
Group B	x	x	0.xx	0.xx, 0.xx		

Implementation Notes:

Depending on the observed test statistic value, the last two columns will be rounded accordingly. The appropriate critical value (positive vs. negative) will be displayed according to the sign of the test statistic.

Table 13: Microbiologic Cure at Visit 3 (Day 29) by Treatment Group - CC Population

Treatment Group	Number of Subjects with Microbiologic Cure n	Number of Subjects N	Proportion of Subjects with Microbiologic Cure	Proportion of Subjects with Microbiologic Cure 95% CI	Difference in Proportion of Subjects with Microbiologic Cure between Doxycycline and Azithromycin	Difference in Proportion of Subjects with Microbiologic Cure between Doxycycline and Azithromycin 95% CI	Test Statistic	Critical Value	P-Value[a]
Doxycycline	x	x	0.xx	0.xx, 0.xx	0.xx	0.xx, 0.xx	x.x	+/- 1.97743	0.xxx
Azithromycin	x	x	0.xx	0.xx, 0.xx					
All Subjects	x	x	0.xx	0.xx, 0.xx					

Note: The denominator for proportions is based on the number of subjects enrolled in the respective treatment group.
[a] P-value from the two-sided Pearson Chi-Square test.

Implementation Notes:

Depending on the observed test statistic value, the last two columns will be rounded accordingly. The appropriate critical value (positive vs. negative) will be displayed according to the sign of the test statistic.

Tables with similar format:

Table 14: Microbiologic Cure at Visit 3 (Day 29) by Treatment Group - ITT Population

Table 15: Microbiologic Cure at Visit 3 (Day 29) by Treatment Group - PP Population

Table 16: Microbiologic Cure at Visit 2 (Day 15) by Treatment Group - CC Population

Table 17: Microbiologic Cure at Visit 2 (Day 15) by Treatment Group - ITT Population

Table 18: Microbiologic Cure at Visit 2 (Day 15) by Treatment Group - PP Population

Implementation Notes:

Test Statistic and Critical Value columns are not applicable for Table 14 to Table 18 and thus will be excluded.

Table 19: Microbiologic Cure at Visit 3 (Day 29) by Treatment Group and Baseline LGV Infection Status - CC Population

Treatment Group	Number of Subjects with Microbiologic Cure n	Number of Subjects N	Proportion of Subjects with Microbiologic Cure	Proportion of Subjects with Microbiologic Cure 95% CI	Difference in Proportion of Subjects with Microbiologic Cure between Doxycycline and Azithromycin	Difference in Proportion of Subjects with Microbiologic Cure between Doxycycline and Azithromycin 95% CI
LGV Negative						
Doxycycline	x	x	0.xx	0.xx, 0.xx	0.xx	0.xx, 0.xx
Azithromycin	x	x	0.xx	0.xx, 0.xx		
All Subjects	x	x	0.xx	0.xx, 0.xx		
LGV Positive						
Doxycycline	x	x	0.xx	0.xx, 0.xx	0.xx	0.xx, 0.xx
Azithromycin	x	x	0.xx	0.xx, 0.xx		
All Subjects	x	x	0.xx	0.xx, 0.xx		

Note: The denominator for proportions is based on the number of subjects enrolled in the respective treatment group.

Tables with similar format:

Table 20: Microbiologic Cure at Visit 3 (Day 29) by Treatment Group and Baseline LGV Infection Status - ITT Population

Table 21: Microbiologic Cure at Visit 3 (Day 29) by Treatment Group and Baseline LGV Infection Status - PP Population

Table 22: Microbiologic Cure at Visit 2 (Day 15) by Treatment Group and Baseline LGV Infection Status - CC Population

Table 23: Microbiologic Cure at Visit 2 (Day 15) by Treatment Group and Baseline LGV Infection Status - ITT Population

Table 24: Microbiologic Cure at Visit 2 (Day 15) by Treatment Group and Baseline LGV Infection Status - PP Population

Table 25: Microbiologic Cure at Visit 3 (Day 29) by Treatment Group and Baseline HIV Status - CC Population

Table 26: Microbiologic Cure at Visit 3 (Day 29) by Treatment Group and Baseline HIV Status -ITT Population

Table 27: Microbiologic Cure at Visit 3 (Day 29) by Treatment Group and Baseline HIV Status - PP Population

Table 28: Microbiologic Cure at Visit 3 (Day 29) by Treatment Group and Adherence to Treatment - CC Population

Table 29: Microbiologic Cure at Visit 3 (Day 29) by Treatment Group and Adherence to Treatment - ITT Population

Table 30: Microbiologic Cure at Visit 3 (Day 29) by Treatment Group and Adherence to Treatment - PP Population

Table 31: Microbiologic Cure at Visit 3 (Day 29) by Treatment Group and Use of Antacids - CC Population

Table 32: Microbiologic Cure at Visit 3 (Day 29) by Treatment Group and Use of Antacids - ITT Population

Table 33: Microbiologic Cure at Visit 3 (Day 29) by Treatment Group and Use of Antacids - PP Population

Table 34: Microbiologic Cure at Visit 3 (Day 29) by Treatment Group and Baseline Symptomatic Status - CC Population

Table 35: Microbiologic Cure at Visit 3 (Day 29) by Treatment Group and Baseline Symptomatic Status - ITT Population

Table 36: Microbiologic Cure at Visit 3 (Day 29) by Treatment Group and Baseline Symptomatic Status - PP Population

Implementation Notes:

For Tables 26 – 28, the subgroup labels will be “HIV Negative” and “HIV Positive”.

For Tables 29 – 31, four subgroups will be included in the summaries, two for the primary definition of adherence (with subgroup labels “Adherent – Primary Def’n” and “Not Adherent – Primary Def’n”) and two for the alternative definition of adherence (with subgroup labels “Adherent – Alternate Def’n” and “Not Adherent – Alternate Def’n”).

For Tables 32 – 34, the subgroup labels will be “No Antacid Use” and “Antacid Use”.

For Tables 35 – 37, the subgroup labels will be “Asymptomatic” and “Symptomatic”.

Table 37: Summary of Categorical Demographic and Baseline Characteristics by Site - All Enrolled Subjects

Variable	Characteristic	University of Washington (N=X)		Fenway Health (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Ethnicity	Not Hispanic or Latino	x	x	x	x	x	x
	Hispanic or Latino	x	x	x	x	x	x
	Not Reported	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x
Race	American Indian or Alaska Native	x	x	x	x	x	x
	Asian	x	x	x	x	x	x
	Native Hawaiian or Other Pacific Islander	x	x	x	x	x	x
	Black or African American	x	x	x	x	x	x
	White	x	x	x	x	x	x
	Multi-Racial	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x
Rectal CT Symptomatic Status	Symptomatic	x	x	x	x	x	x
	Asymptomatic	x	x	x	x	x	x
Inguinal Lymphadenopathy	Yes	x	x	x	x	x	x
	No	x	x	x	x	x	x

Note: N=Number of subjects enrolled at the specified site.

Table 38: Summary of Categorical Demographic and Baseline Characteristics by Treatment Group- ITT Population

Variable	Characteristic	Azithromycin (N=X)		Doxycycline (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Ethnicity	Not Hispanic or Latino	x	x	x	x	x	x
	Hispanic or Latino	x	x	x	x	x	x
	Not Reported	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x
Race	American Indian or Alaska Native	x	x	x	x	x	x
	Asian	x	x	x	x	x	x
	Native Hawaiian or Other Pacific Islander	x	x	x	x	x	x
	Black or African American	x	x	x	x	x	x
	White	x	x	x	x	x	x
	Multi-Racial	x	x	x	x	x	x
	Unknown	x	x	x	x	x	x
Rectal CT Symptomatic Status	Symptomatic	x	x	x	x	x	x
	Asymptomatic	x	x	x	x	x	x
Inguinal Lymphadenopathy	Yes	x	x	x	x	x	x
	No	x	x	x	x	x	x

Note: N=Number of Subjects in the ITT population randomized to the specified treatment group.

Table 39: Summary of Continuous Demographic and Baseline Characteristics by Site - All Enrolled Subjects

Variable	Statistic	University of Washington (N=X)	Fenway Health (N=X)	All Subjects (N=X)
Age	Mean	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x
	Median	x.x	x.x	x.x
	Minimum	x	x	x
	Maximum	x	x	x

Note: N=Number of subjects enrolled at the specified site.

Table 40: Summary of Continuous Demographic and Baseline Characteristics by Treatment Group - ITT Population

Variable	Statistic	Azithromycin (N=X)	Doxycycline (N=X)	All Subjects (N=X)
Age	Mean	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x
	Median	x.x	x.x	x.x
	Minimum	x	x	x
	Maximum	x	x	x

Note: N=Number of subjects in the ITT population randomized to the specified treatment group.

Table 41: Summary of Baseline STD and Sexual History - ITT Population

Interview Item	Response	Azithromycin (N=X)		Doxycycline (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Any STD in the 60 days prior to enrollment	Yes	x	x	x	x	x	x
	No	x	x	x	x	x	x
Number of male sexual partners in the past 60 days	0	x	x	x	x	x	x
	1	x	x	x	x	x	x
	2-10	x	x	x	x	x	x
	>10	x	x	x	x	x	x
Receptive anal sex in the past week	Yes	x	x	x	x	x	x
	No	x	x	x	x	x	x
Use of condoms for receptive anal sex in the past week[a]	Always	x	x	x	x	x	x
	Sometimes/Never	x	x	x	x	x	x
Receptive anal sex in the past 60 days	Yes	x	x	x	x	x	x
	No	x	x	x	x	x	x
Rimming in the past 60 days	Yes	x	x	x	x	x	x
	No	x	x	x	x	x	x
Fisting in the past 60 days	Yes	x	x	x	x	x	x
	No	x	x	x	x	x	x
Use of any lubricant for receptive anal sex	Yes	x	x	x	x	x	x
	No	x	x	x	x	x	x
Lubricants used[a]	Saliva	x	x	x	x	x	x
	Ejaculate	x	x	x	x	x	x
	Water-Based	x	x	x	x	x	x
	Silicone-Based	x	x	x	x	x	x
	Oil	x	x	x	x	x	x
	None	x	x	x	x	x	x
	Other/Unknown	x	x	x	x	x	x

Interview Item	Response	Azithromycin (N=X)		Doxycycline (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Use of rectal douches or enemas in the past 60 days	Yes	x	x	x	x	x	x
	No	x	x	x	x	x	x
Douches/Enemas Used[a]	Water	x	x	x	x	x	x
	Fleet Enema	x	x	x	x	x	x
	Mineral Oil	x	x	x	x	x	x
	Other	x	x	x	x	x	x

Note: N=Number of Subjects in the ITT population randomized to the specified treatment group and who have STD and sexual history data available.
[a]: The denominator for percentages is the number of subjects who responded 'Yes' to the previous question.

Tables with similar format:

Table 42: Summary of Follow-Up STD and Sexual History - ITT Population

Implementation Notes:

For Yes/No responses, a subject will be classified as 'Yes' if he answered 'Yes' at either Visit 2 or Visit 3. For other response types, a subject will be included in each count if he provided the response at either Visit 2 or 3.

Table 43: Summary of Antiretroviral and PrEP Use - ITT Population

HIV Classification	Summary	Azithromycin (N=X)		Doxycycline (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
HIV positive subjects at baseline	Number of Subjects	x	-	x	-	x	-
	Currently taking Antiretroviral Therapy	x	x	x	x	x	x
	Not taking Antiretroviral Therapy	x	x	x	x	x	x
HIV positive during follow-up	Number of Subjects	x	-	x	-	x	-
	Currently taking Antiretroviral Therapy	x	x	x	x	x	x
	Not taking Antiretroviral Therapy	x	x	x	x	x	x
HIV negative at baseline	Number of Subjects	x	-	x	-	x	-
	Currently taking PrEP	x	x	x	x	x	x
	Not taking PrEP	x	x	x	x	x	x
HIV negative during follow-up	Number of Subjects	x	-	x	-	x	-
	Currently taking PrEP	x	x	x	x	x	x
	Not taking PrEP	x	x	x	x	x	x

Notes: N=Number of Subjects in the ITT population randomized to the specified treatment group.
The denominator for percentages is the number of subjects in the specified treatment group and HIV classification.

Table 44: Adverse Effects Due to Drug Intolerance

Summary	Visit 2 (N=X)				Visit 3 (N=X)				Unscheduled Visit/Early Termination Visit (N=X)			
	Azithromycin (N=X)		Doxycycline (N=X)		Azithromycin (N=X)		Doxycycline (N=X)		Azithromycin (N=X)		Doxycycline (N=X)	
Nausea	x	x	x	x	x	x	x	x	x	x	x	x
Vomiting	x	x	x	x	x	x	x	x	x	x	x	x
Diarrhea	x	x	x	x	x	x	x	x	x	x	x	x
Dysphagia	x	x	x	x	x	x	x	x	x	x	x	x
Abdominal pain	x	x	x	x	x	x	x	x	x	x	x	x
Rash	x	x	x	x	x	x	x	x	x	x	x	x
Other	x	x	x	x	x	x	x	x	x	x	x	x

Notes: N is the number of subjects whose assessments were collected at the particular visit.
'n' represents the number of subjects who reported each sign or symptom at the visit(s) indicated.
The denominator of the percentage is the number of subjects whose assessments were collected at the particular visit.

Table 45: Summary of Study Product Vomiting - ITT Population

	Azithromycin (N=X)		Doxycycline (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%
Was observed taking Initial Dose (Dose 1)	x	-	x	-	x	-
Vomited Initial Dose (Dose 1) within 2 hours of receipt[a]	x	x	x	x	x	x
Returned for Re-treatment	x	-	x	-	x	-
Was observed taking Re-treated Initial Dose (Dose 1)	x	-	x	-	x	-
Vomited Re-treated Dose within 2 hours of receipt[b]	x	x	x	x	x	x

[a] Denominator for percentages is the number of subjects in the specified treatment group that were observed taking Dose 1
[b] Denominator for percentages is the number of subjects in the specified treatment group that were observed taking the re-treated Dose 1

Table 46: Listing of Serious Adverse Events

Adverse Event	Study Day the Event Became Serious (Duration)	Reason Reported as an SAE	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to SAE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Subject ID: , Treatment Group: , AE Number:										
xxxxxxx	**xx (xx)**	**xxxxxx**	**xxxxxx**	**xxxxxx**	**xxxxx**	**xxxxxx**	**Y/N**	**xxxxx**	**xxxxx**	**xxxxx**
Comments: xxxxxxxxxxxxx										
Subject ID: , Treatment Group: , AE Number:										
xxxxxxx	**xx (xx)**	**xxxxxx**	**xxxxxx**	**xxxxxx**	**xxxxx**	**xxxxxx**	**Y/N**	**xxxxx**	**xxxxx**	**xxxxx**
Comments: xxxxxxxxxxxxx										

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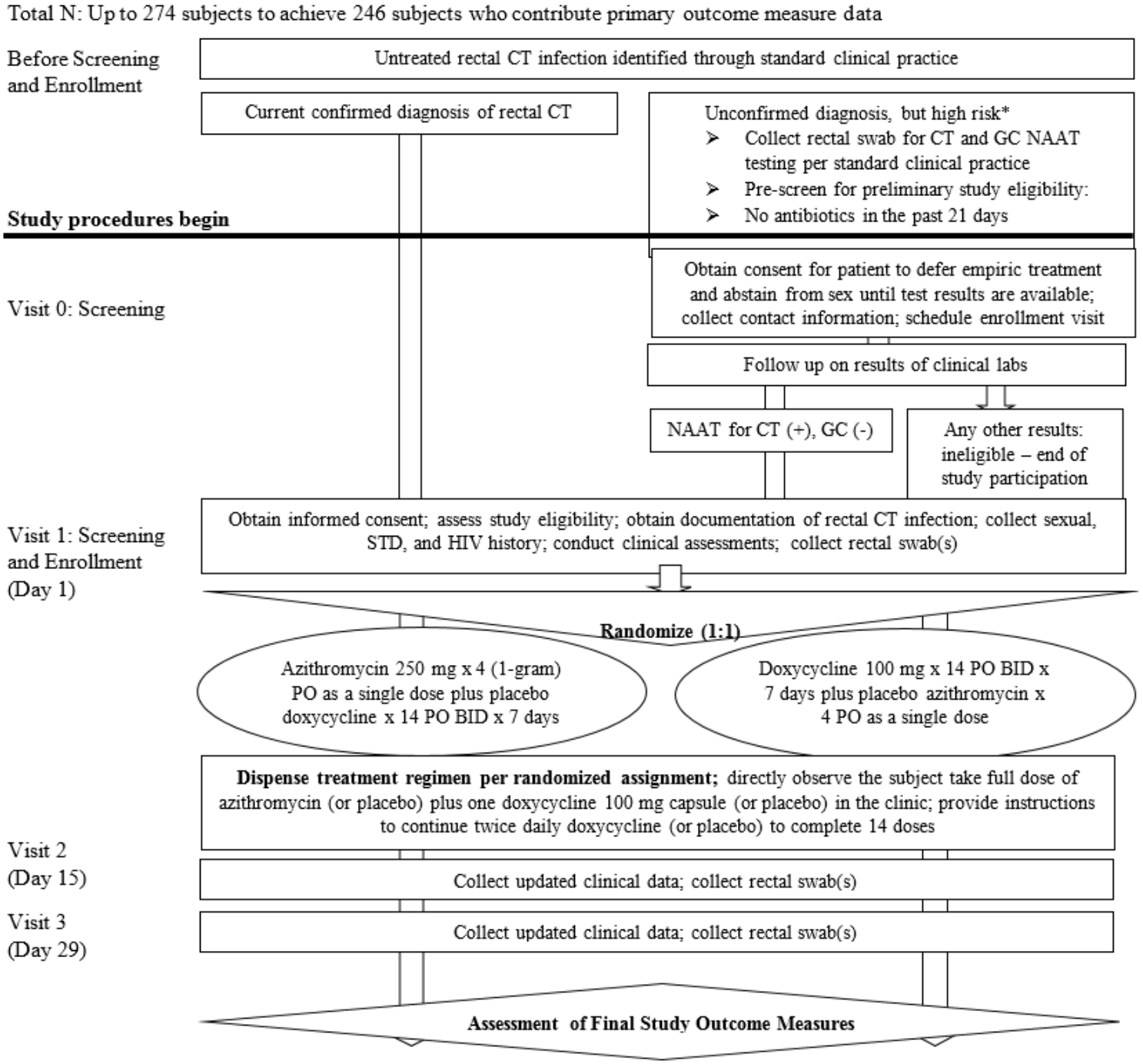
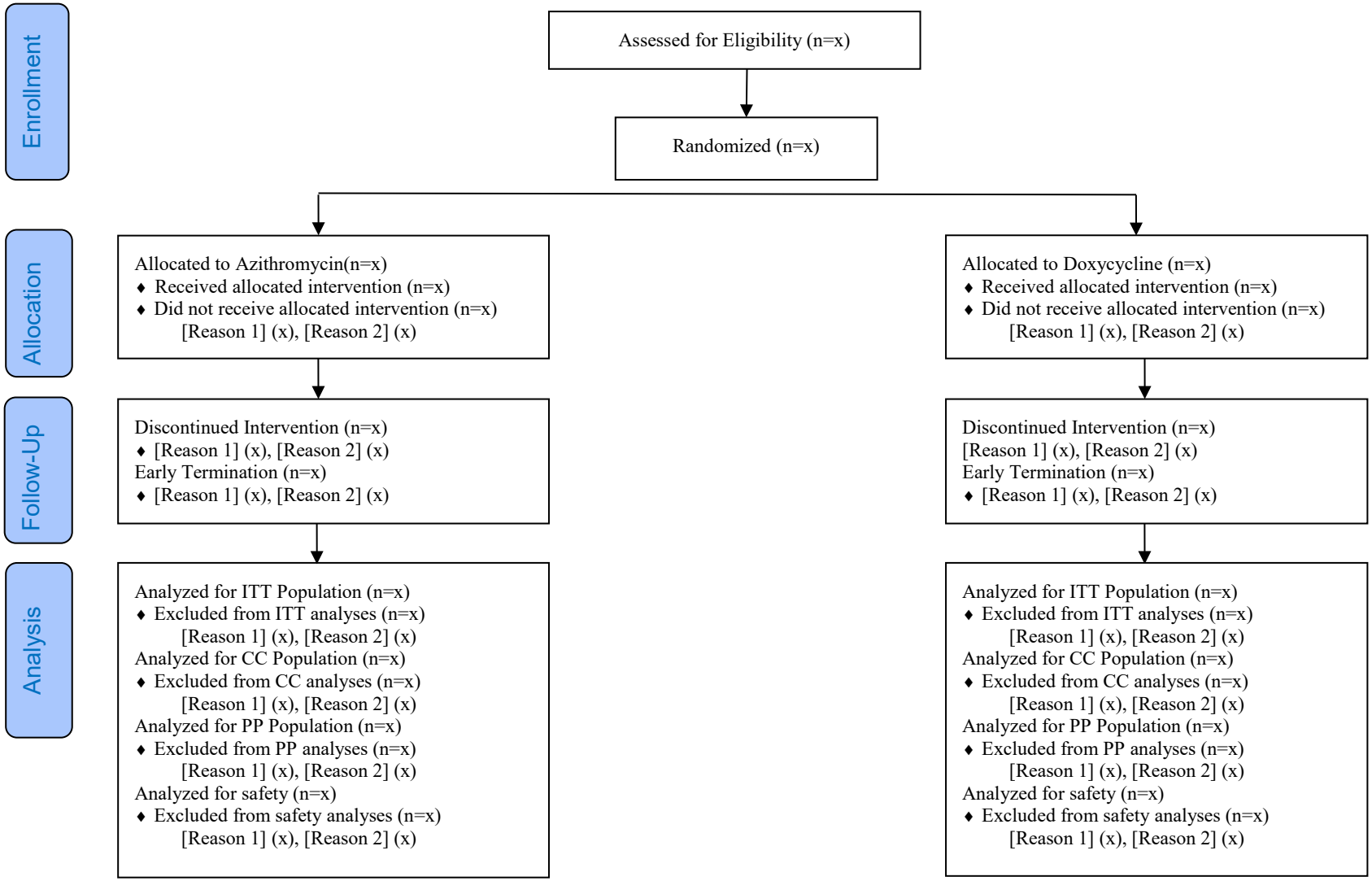
Figure 1: Study Design



*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.

Figure 2: CONSORT Flow Diagram



APPENDIX 3. LISTINGS MOCK-UPS

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Listing 1: Analysis Population Eligibilities

Actual Treatment Group	Randomized Treatment Group	Subject ID	Analyses in which Subject is Included	Analyses from which Subject is Excluded	Microbiological Cure Results Available?	Reason Subject Excluded
Azithromycin/Doxycycline	Azithromycin/Doxycycline	xxxxxx	[e.g., Safety, ITT, CC Day 15, CC Day 29, PP Day 15, PP Day 29]	[e.g., Safety, ITT, CC Day 15, CC Day 29, PP Day 15, PP Day 29]	Day 15: Yes/No Day 29: Yes/No	xxxxxxxx
Azithromycin/Doxycycline	Azithromycin/Doxycycline	xxxxxx	[e.g., Safety, ITT, CC Day 15, CC Day 29, PP Day 15, PP Day 29]	[e.g., Safety, ITT, CC Day 15, CC Day 29, PP Day 15, PP Day 29]	Day 15: Yes/No Day 29: Yes/No	xxxxxxxx
Azithromycin/Doxycycline	Azithromycin/Doxycycline	xxxxxx	[e.g., Safety, ITT, CC Day 15, CC Day 29, PP Day 15, PP Day 29]	[e.g., Safety, ITT, CC Day 15, CC Day 29, PP Day 15, PP Day 29]	Day 15: Yes/No Day 29: Yes/No	xxxxxxxx

Note: "Yes" in the "Microbiological Cure Results available" column indicates that available data were removed from the analysis. If "Yes" the population in which data were removed will be listed in parenthesis. "No" indicates that no data were available for inclusion in the analysis.

Implementation Notes:

1. Sort order will be by Actual Treatment Group, Subject ID.
2. Reasons Subject Excluded should match the same wording that is used on the Analysis population tables.
3. If all subjects received the correct treatment, only display a single "Treatment Group" column.

Listing 2: Subjects Whose Assigned Treatment Group Does Not Match Their Randomized Treatment Group

Subject ID	Treatment Group at Randomization	Treatment Actually Received
xxxxxx	Azithromycin/Doxycycline	Azithromycin/Doxycycline
xxxxxx	Azithromycin/Doxycycline	Azithromycin/Doxycycline

Implementation Note:

1. Sort order is Subject ID.

Listing 3: Early Terminations or Discontinued Subjects – All Enrolled Subjects

Actual Treatment Group	Randomized Treatment Group	Subject ID	Category	Study Day Corresponding to Early Termination/Treatment Discontinuation	Reason for Early Termination or Treatment Discontinuation
Azithromycin/Doxycycline	Azithromycin/Doxycycline	xxxxxx	Early Termination/Treatment Discontinuation	xx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
Azithromycin/Doxycycline	Azithromycin/Doxycycline	xxxxxx	Early Termination/Treatment Discontinuation	xx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
Azithromycin/Doxycycline	Azithromycin/Doxycycline	xxxxxx	Early Termination/Treatment Discontinuation	xx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Implementation Notes:

1. Sort order will be by Actual Treatment Group, Subject ID, Category.
2. If all subjects received the correct treatment, only display a single “Treatment Group” column.
3. Category will be "Early Termination", "Completion" or "Treatment Discontinuation". If a subject discontinued treatment, they will have two records.
4. In the “Reason” column, concatenate any “specify” fields, including AE number and DV number.

Listing 4: Subject-Specific Protocol Deviations

Deviation Number	Study Day	Deviation Description	Deviation Category	Reason for Deviation	Deviation Affected Product Stability?	Deviation Resulted in SAE?	Deviation Resulted in Subject Termination?	Deviation Resolution	Deviation met immediate IRB reporting requirement?	Comments
Actual Treatment Group: , Randomized Treatment Group: , Subject ID:										
xx	xx	xxxxxxx	xxxxxxxxxxx	xxxxxxx	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	xxxxxxxxxxx
xx	xx	xxxxxxx	xxxxxxxxxxx	xxxxxxx	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	xxxxxxxxxxx

Implementation Notes:

1. Sort order will be by Actual Treatment Group, Subject ID, Deviation Number.
2. If all subjects received the correct treatment, only display “Treatment Group”.
3. In the Deviation Description column concatenate any specify fields.
4. In the Reason for Deviation column concatenate any specify fields.

Listing 5: Non-Subject-Specific Protocol Deviations

Site	Deviation Description	Start Day	End Day	Reason for Deviation	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation met immediate IRB reporting requirement?	Deviation Category	Deviation Resolution	Comments
xxxx	xxxx	xx	xx	xxxx	Yes/No	Yes/No/NA	Yes/No	xxxx	xxxx	xxxx
xxxx	xxxx	xx	xx	xxxx	Yes/No	Yes/No/NA	Yes/No	xxxx	xxxx	xxxx

Implementation Notes:

1. Sort order will be by Site, Start Day.
2. In the Deviation Description column concatenate any specify fields.
3. In the Reason for Deviation column concatenate any specify fields.

Listing 6: Individual Efficacy Response Data- All Enrolled Subjects

Actual Treatment Group	Randomized Treatment Group	Subject ID	Baseline LGV Infection Status	Baseline HIV Status	Visit 2 (Day 15) Rectal CT NAAT Result	Visit 3 (Day 29) Rectal CT NAAT Result
Azithromycin/ Doxycycline	Azithromycin/ Doxycycline	xxxxxx	Non-LGV/LGV/Indeterminate/Not Done	Negative/ Positive/Unknown	Negative/Positive/ Indeterminate/Not Done	Negative/Positive/ Indeterminate/Not Done
Azithromycin/ Doxycycline	Azithromycin/ Doxycycline	xxxxxx	Non-LGV/LGV/Indeterminate/Not Done	Negative/ Positive/Unknown	Negative/Positive/ Indeterminate/Not Done	Negative/Positive/ Indeterminate/Not Done

Implementation Notes:

1. Sort order will be by Actual Treatment Group, Subject ID, Baseline LGV Infection Status.
2. If all subjects received the correct treatment, only display a single “Treatment Group” column.

Listing 7: Demographic and Baseline Characteristics - All Enrolled Subjects

Actual Treatment Group	Randomized Treatment Group	Subject ID	Age at Enrollment (years)	Ethnicity	Race	Symptomatic Status	Inguinal Lymphadenopathy
Azithromycin/Doxycycline	Azithromycin/Doxycycline	xxxxxx	xx	xxxxxx	xxxxxx	Symptomatic/ Asymptomatic	Yes/No
Azithromycin/Doxycycline	Azithromycin/Doxycycline	xxxxxx	xx	xxxxxx	xxxxxx	Symptomatic/ Asymptomatic	Yes/No

Implementation Notes:

1. Sort order will be by Actual Treatment Group, Subject ID.
2. For the Race column, if a subject is Multi-Racial, all races will be listed, separated by a comma.
3. If subject was a screen failure, populate Actual Treatment Group and Randomized Treatment Group with "—".
4. If all subjects received the correct treatment, only display a single "Treatment Group" column.

Listing 8: STD History - All Enrolled Subjects

Timepoint	Diagnosed STDs[a] (Start Date / End Date)	Self-Reported HIV Status[b] (Date of Testing or Diagnosis)	On Antiretroviral Therapy?[c]
Actual Treatment Group: , Randomized Treatment Group: , Subject ID:			
Baseline	Chlamydia/Gonorrhea/ Syphilis/Specify (ddMMMyyyy / ddMMMyyyy / Ongoing)	Positive/Negative (ddMMMyyyy / Not Reported)	Yes/No/NA
Post-baseline	Chlamydia/Gonorrhea/ Syphilis/Specify (ddMMMyyyy / ddMMMyyyy / Ongoing)	Positive/Negative (ddMMMyyyy / Not Reported)	Yes/No/NA

[a] At baseline, the timeframe for recorded diagnoses is 60 days prior to enrollment. At Visit 2, the timeframe is since Visit 1. At Visit 3, the timeframe is anytime during the trial.
[b] Post-baseline HIV status only recorded if the subject reported being tested during the study.
[c] Applicable to subjects who are HIV positive only.

Implementation Notes:

1. Sort order will be by Actual Treatment Group, Subject ID.
2. If all subjects received the correct treatment, only display "Treatment Group".
3. If a subject has multiple testing dates and/or results or multiple reported STDs then each test and/or STD will have its own row. If the occurrence was recorded at Baseline, the Timepoint will be "Baseline". If the occurrence was recorded post-baseline, the Timepoint will be "Post-baseline".

Listing 9: Sexual History - All Enrolled Subjects

Timepoint	Number of Male Sexual Partners[a]	Has Had Anal Receptive Sex				Has Been Rimmed / Fisted?	Lubricants Used for Receptive Anal Sex	Rectal Douches/Enemas Used	Use of Rectal Douches/Enemas in Relation to Sexual Activity	Was Douching Equipment Shared with Anyone?
		Type of Partner	Number of Partners[a]	Partner Initiated Treatment for CT? (How Often was a Condom Used?)	Partner Did Not Initiate Treatment for CT? (How Often was a Condom Used?)					
Actual Treatment Group: , Randomized Treatment Group: , Subject ID:										
Screening	x	"New" Partners	x/NA	Yes/No/NA (Always/Sometimes/Never)	N/A	Yes/No Yes/No	xxxx, xxxx, xxxx,	xxxx, xxxx, xxxx,	xxxx, xxxx, xxxx,	Yes/No
		"Previous" Partners	x/NA	Yes/No/NA (Always/Sometimes/Never)	N/A					
Visit 2	x	"New" Partners	x/NA	Yes/No/NA (Always/Sometimes/Never)	Yes/No (Always/Sometimes/ Never)	Yes/No Yes/No	xxxx, xxxx, xxxx,	xxxx, xxxx, xxxx,	xxxx, xxxx, xxxx,	Yes/No
		"Previous" Partners	x/NA	Yes/No/NA (Always/Sometimes/Never)	Yes/No (Always/Sometimes/ Never)					
Visit 3	x	"New" Partners	x/NA	Yes/No/NA (Always/Sometimes/Never)	Yes/No (Always/Sometimes/ Never)	Yes/No Yes/No	xxxx, xxxx, xxxx,	xxxx, xxxx, xxxx,	xxxx, xxxx, xxxx,	Yes/No
		"Previous" Partners	x/NA	Yes/No/NA (Always/Sometimes/Never)	Yes/No (Always/Sometimes/ Never)					

[a] The timeframe for the number of Sexual Partners is "in the past 60 days" (prior to enrollment). The timeframe at the screening visit for the Number of New Partners is "in the past week", while the timeframe for the Number of Previous Partners is "in the past 60 days". The timeframe for the Number of New and Previous Partners at the follow-up visits is "since the last visit".

Implementation Notes:

1. Sort order will be by Actual Treatment Group, Subject ID.
2. If all subjects received the correct treatment, only display "Treatment Group".
3. If the subject reported no anal receptive sex, then the corresponding anal receptive sex cells will all be "NA".
4. Missing responses will be populated with "Not Reported".

Listing 10: Concomitant Medications - All Enrolled Subjects

Actual Treatment Group	Randomized Treatment Group	Subject ID	Concomitant Medication Number	Medication	Medication Start Day	Medication End Day	Indication	ATC 1 / ATC 2	Taken for a SAE? (AE Description; AE Number)	Taken for HIV or an STD?
Azithromycin/Doxycycline	Azithromycin/Doxycycline	xxxxxx	xx	xxxxxx	xx	xx	xxxxxx	xxxx / xxxx	Yes/No xxxxx; xx	Yes/No
Azithromycin/Doxycycline	Azithromycin/Doxycycline	xxxxxx	xx	xxxxxx	xx	xx	xxxxxx	xxxx / xxxx	Yes/No xxxxx; xx	Yes/No

Implementation Notes:

1. Sort order will be by Actual Treatment Group, Subject ID, Concomitant Medication Number.
2. Medication Start Day' and 'Medication End Day' are relative to enrollment (which is Day 1, day before enrollment is Day -1). For medication start dates that are > 30 days prior to enrollment, rather than use exact days, categorize as follows:

   - > 5 years prior to enrollment

   - 1- 5 years prior to enrollment

   - 1-12 months (exclusive of 12 months) prior to enrollment.

   - For 'Medication End Day', if medication is ongoing, display 'Ongoing' in the Medication End Day' column.

   - For 'Medication End Day', if end of medication is unknown, display 'Unknown' in the 'Medication End Day' column.
3. If a Medication is taken for a SAE, then concatenate the conmed with the Adverse Events by AENUM and report the AETERM.
4. If all subjects received the correct treatment, only display a single “Treatment Group” column.

Listing 11: Treatment Adherence Data

Actual Treatment Group	Randomized Treatment Group	Subject ID	Initial Dose of Azithromycin or Placebo Taken?	Initial Dose of Doxycycline or Placebo Taken?	Vomited Within 2 Hours of Receiving Study Treatment at Visit 01?	Returned to the Clinic for Retreatment of the First Dose?	Vomited Within 2 Hours of Receiving Study Treatment at the Retreatment Visit?	Days to Finish the Total Number of Doxycycline or Placebo Capsules	Number of Doxycycline or Placebo Capsules Taken by the End of the 7th Day	Number of Doxycycline or Placebo Capsules Taken by the End of the 10th Day	Compliance Status (Primary Definition)	Compliance Status (Alternate Definition)
Azithromycin/ Doxycycline	Azithromycin/ Doxycycline	xxxxxx	Yes/No	Yes/No	Yes/No	Yes/No/ NA	Yes/No/ NA	x	x	x	Compliant/ Non-compliant	Compliant/ Non-compliant
Azithromycin/ Doxycycline	Azithromycin/ Doxycycline	xxxxxx	Yes/No	Yes/No	Yes/No	Yes/No/ NA	Yes/No/ NA	x	x	x	Compliant/ Non-compliant	Compliant/ Non-compliant

Implementation Notes:

1. Sort order will be by Actual Treatment Group, Subject ID.
2. If all subjects received the correct treatment, only display a single “Treatment Group” column.
3. Vomited doses will not be included in the “Number of Capsules Taken…” counts.

Listing 12: Adverse Effects Due to Drug Intolerance

Actual Treatment Group	Randomized Treatment Group	Subject ID	Assessment Study Day	Adverse Effects Due to Drug Intolerance
Azithromycin/Doxycycline	Azithromycin/Doxycycline	xxxxxx	xx	Nausea/Vomiting/Diarrhea/Dysphagia/Abdominal Pain/Rash/Other: XXX
Azithromycin/Doxycycline	Azithromycin/Doxycycline	xxxxxx	xx	Nausea/Vomiting/Diarrhea/Dysphagia/Abdominal Pain/Rash/Other: XXX

Implementation Notes:

1. If a subject has more than one event, each event will be displayed in its own row.
2. Sort order will be by Actual Treatment Group, Subject ID, Study Day.
3. Concatenate the “specify” fields if applicable.
4. If all subjects received the correct treatment, only display a single “Treatment Group” column.

Listing 13: Physical Exam Findings

Actual Treatment Group	Randomized Treatment Group	Subject ID	Study Day	Body System	Abnormal Finding	Reported as an SAE?	AE Number
Azithromycin/Doxycycline	Azithromycin/Doxycycline	xxxxxx	xx	xxx	xxxxxxxxxxxxxxxxxxxx	No/Yes	xx
Azithromycin/Doxycycline	Azithromycin/Doxycycline	xxxxxx	xx	xxx	xxxxxxxxxxxxxxxxxxxx	No/Yes	xx

Implementation Notes:

1. If a subject has more than one finding, then each finding will be listed in its own row.
2. Sort order will be by Actual Treatment Group, Subject ID, Study Day.
3. Only abnormal findings will be presented.
4. If all subjects received the correct treatment, only display a single “Treatment Group” column.