Treatment Failure and Associated Predictors Following Azithromycin Treatment for Urogenital Chlamydial Infection in Males in Youth Correctional Facilities

DMID Protocol Number: 16-0002

DMID Funding Mechanism: 2722013000121

Principal Investigator: William M. Geisler, MD, MPH

DMID Clinical Project Manager: Barbara Hahn, RN, BSN

Draft or Version Number: Version 3.0

05 October 2017

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) and the applicable regulatory requirements:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46; 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)
- ICH E6; 62 Federal Register 25691 (1997)
- NIH Clinical Terms of Award
- Completion of Human Subjects Protection Training
- California laws and regulations

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator: William M. Geisler, MD, MPH

Signed: _____ Date: _____

Name: William M. Geisler, MD, MPH
Title: Professor of Medicine, UAB

Site Investigator: Raymond Perry, MD, MSHS

Signed: _____ Date: _____

Name: Raymond Perry, MD, MSHS
Title: Los Angeles County Department of Health Services

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

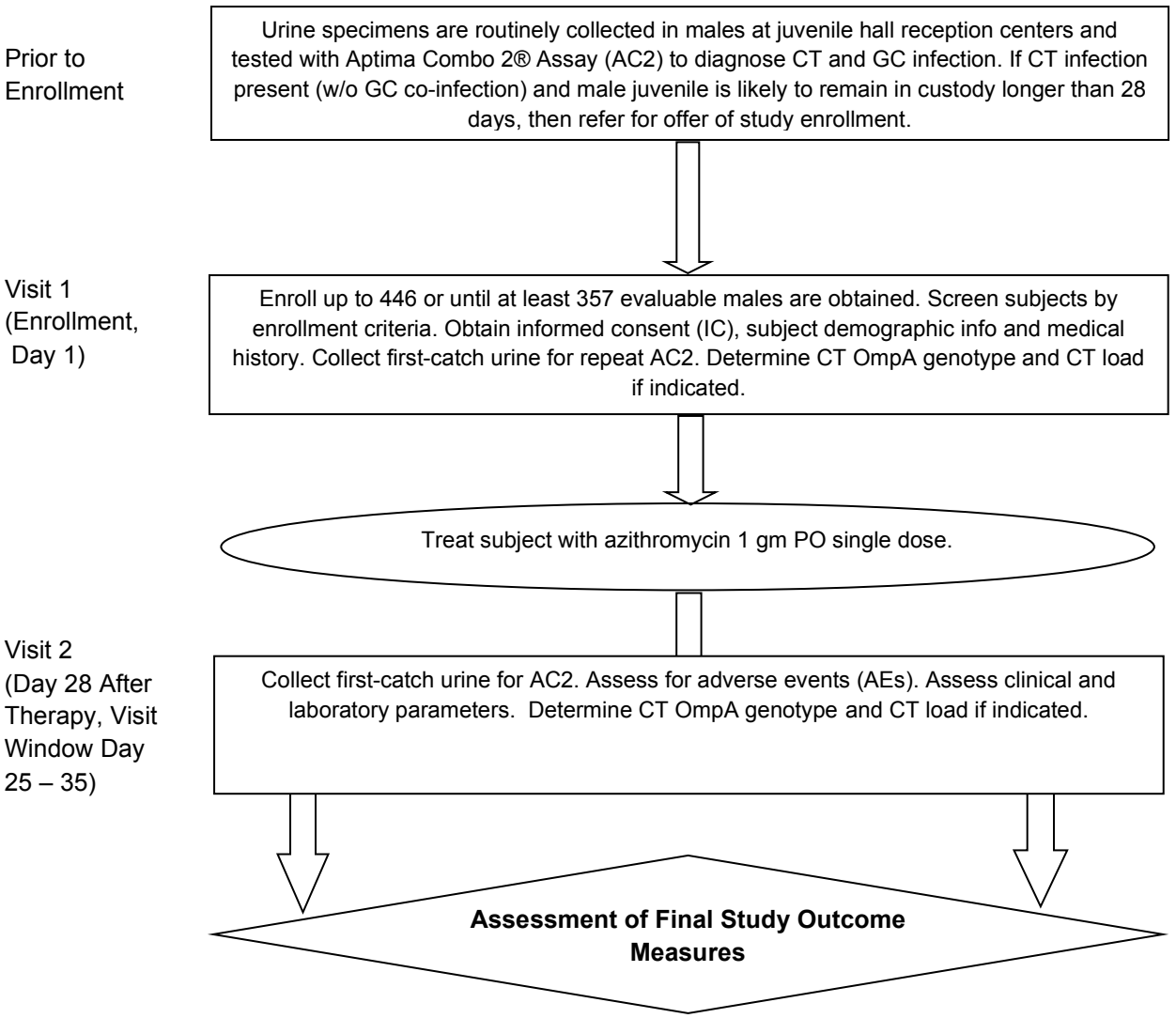
AC2	Aptima Combo 2® Assay
AE	Adverse Event/Adverse Experience
BID	Twice a day
CDC	Centers for Disease Control and Prevention
CDM	Center for Data Management
CI	Confidence Interval
CFR	Code of Federal Regulations
CPM	Clinical Project Manager
CRF	Case Report Form
CROMS	Clinical Research Operations and Management Support
CT	*Chlamydia Trachomatis*
DHHS	Department of Health and Human Services
DM plan	Data Management Plan
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data and Safety Monitoring Board
EMR	Electronic Medical Record
FDA	Food and Drug Administration
GC	*Neisseria Gonorrhoeae*
GCP	Good Clinical Practice
gm	Gram
HIV	Human Immunodeficiency Virus
IC	Informed Consent
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
LA	Los Angeles
LACDPH	Los Angeles County Department of Public Health
MedDRA ®	Medical Dictionary for Regulatory Activities
mg	Milligrams
NAAT	Nucleic Acid Amplification Test
NGU	Nongonococcal Urethritis
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OmpA	Major Outer Membrane Protein
PCR	Polymerase Chain Reaction
PD	Protocol Deviation
PI	Principal Investigator

PO	By mouth
PS	Protocol Specialist
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SAS	Statistical Analysis Software
SC	Study Coordinator
SI	Site Investigator
SOP	Standard Operating Procedure
STD	Sexually Transmitted Disease
STI	Sexually Transmitted Infection
STI CTG	Sexually Transmitted Infection Clinical Trials Group
UAB	University of Alabama at Birmingham
US	United States
USC	University of Southern California
WHO	World Health Organization
YCF	Youth Correctional Facility

PROTOCOL SUMMARY

Title:	Evaluation of Treatment Failure and Associated Predictors Following Azithromycin Treatment for Urogenital Chlamydial Infection in Males in Youth Correctional Facilities (YCFs)
Phase:	Not applicable
Population:	Up to 446 males ages 12-21 in good health identified as chlamydia-infected through screening who are residing in long-term gender-segregated YCFs in Los Angeles County.
Number of Sites:	1 site which is comprised of the Los Angeles County Department of Public Health and 15 YCFs located within Los Angeles County: Los Padrinos Juvenile Hall; Central Juvenile Hall; Barry J. Nidorf Juvenile Hall; Dorothy Kirby Center; Camp Afflerbaugh; Camp David Gonzales; Camp Joseph Paige; Camp Glenn Rockey; Camp Gregory Jarvis; Camp Ronald McNair; Camp Ellison Onizuka; Camp Judith Resnik; Camp Francis J. Scobee; Camp Michael Smith; and Camp Kilpatrick
Study Duration:	4 years
Subject Participation Duration:	28 days
Description of Agent or Intervention:	Azithromycin (1 gm PO single dose) for the treatment of urogenital chlamydia
Objectives:	Primary: Assess the microbiological efficacy of azithromycin in uncomplicated *Chlamydia trachomatis* infection in males with versus without urethral symptoms in YCFs; in essence, this study will assess the frequency of chlamydia treatment failure to azithromycin at the Day 28 follow-up visit (Visit 2) in males with urethral symptoms compared to males without urethral symptoms. Secondary: Evaluate the association of laboratory findings (enrollment chlamydia load and OmpA genotype) and other participant characteristics (demographics, sexual behaviors, etc.) to chlamydia treatment failure in males after azithromycin treatment.
Estimated Time to Complete Enrollment:	3.3 years

Description of Study Design:



1 KEY ROLES

For questions regarding this protocol, contact: Barbara Hahn (Clinical Project Manager) at 240-627-3267

Individuals:

DMID Clinical Project Manager
Barbara Hahn, RN, BSN
STD Branch, DMID, NIAID, NIH
5601 Fishers Lane, Rm 8E49
Bethesda, MD, 20892-9825
(for FedEx, UPS, DHL use Rockville, MD, 20852)
Phone: 240-627-3267
bhahn@niaid.nih.gov

Principal Investigator
William M. Geisler, MD, MPH
University of Alabama at Birmingham
Zeigler Research Building 242
703 19th St South
Birmingham, AL 35294-0007
Phone: (205) 934-4376
Fax: (205) 975-7764
E-mail: wgeisler@uabmc.edu

DMID Medical Monitor
Soju Chang, MD, MPH
DMID/NIAID/NIH
5601 Fishers Lane, Rm 7E59
Bethesda, MD 20892-9825
Phone: (240) 292-4178
Email: changsoju@niaid.nih.gov

Site Investigator
Raymond C.W. Perry, MD, MSHS
Los Angeles County Department of Health Services
1925 Daly Street, 1st floor
Los Angeles, CA 90031
Office Phone: (323) 897-6300
Fax: (323) 226-5746
Email: rperry@dhs.lacounty.gov

Site Sub-Investigator
David Oh, MD
Medical Director, Juvenile Court Health Services
1925 Daly St., 1st floor
Los Angeles, CA 90031
Office Phone: (323) 226 – 8723
Fax: (323) 226-5746
Email: doh@dhs.lacounty.gov

Protocol Specialist
Anne Rinaldi
FHI 360
359 Blackwell Street, Suite 200
Durham, NC 27701
Phone: (919) 544-7040, x 11497
Fax: (919) 544-7261
E-mail: arinaldi@fhi360.org

Protocol Data Manager
Lalitha Venkatasubramanian
359 Blackwell Street, Suite 200
Durham, NC 27701
Phone: (919) 544-7040, x 11338
Fax: (919) 544-7261
E-mail: lvenkat@fhi360.org

Protocol Statistician
Jeannette Y. Lee, PhD
Professor, Department of Biostatistics
University of Arkansas for Medical Sciences
4301 West Markham Street, #781
Little Rock, Arkansas 72205
Phone: (501) 526-6712
Fax: (501) 526-6729
E-mail: jylee@uams.edu

Institutions:

Los Angeles County Department of Public Health Institutional Review Board
J. Walton Senterfitt, PhD, Chairman
313 N. Figueroa Street, Room 227
Los Angeles, CA 90012
Phone: (213) 250-8639
Fax: (213) 481-9853
E-mail: jsenterfitt@ph.lacounty.gov

University of Alabama Institutional Review Board for Human Use
University of Alabama at Birmingham
470 Administration Building
1530 3rd Avenue South
Birmingham, AL 35294-0104
Phone: (205) 934-3789
Fax: (205) 934-1301

William Geisler Chlamydia Laboratory
University of Alabama at Birmingham
703 19th St South, 242 Zeigler Research Building
Birmingham, AL 35294-0007
Phone: (205) 934-4376
Fax: (205) 975-7764

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Chlamydia trachomatis infection (chlamydia) is a public health concern. The World Health Organization (WHO) estimates there are >105 million new cases of chlamydia annually.[1] In the U.S. alone, approximately 3 million new cases of chlamydia are reported yearly, and the costs associated with their management and complications exceed $2 billion.[2] Chlamydia can spread to the upper urogenital tract, which can cause significant morbidity. Chlamydia is a leading preventable cause of infertility worldwide. Inflammation associated with urogenital chlamydia can also increase the risk of acquisition and transmission of human immunodeficiency virus (HIV). In many populations, the majority of chlamydia-infected individuals are asymptomatic,[3] and unless the infection is detected through chlamydial testing (screening), their infection may be missed and transmitted to others or lead to complications. Chlamydia testing can now be performed on non-invasively collected specimens (e.g., urine) using sensitive and specific nucleic acid amplification tests (NAATs), which should facilitate screening in nontraditional clinical settings (e.g., correctional facilities).

The Centers of Disease Control and Prevention (CDC) recommends either azithromycin 1 gram (gm) by mouth (PO) once or doxycycline 100 milligrams (mg) PO twice daily (BID) for 7 days as co-equal therapies for uncomplicated chlamydia.[4] This recommendation is supported by a meta-analysis by Lau et al. of 12 randomized clinical trials of azithromycin versus doxycycline for urogenital chlamydial infections, in which microbial cure rates (based on chlamydia culture in 9 of the 12 trials) were 97% and 98%, respectively, and after pooling the data, the efficacy difference for microbial cure between the 2 drugs was not statistically significant.[5] However, most efficacy studies of therapy for chlamydia relied on measuring outcome (i.e., test of cure) using diagnostic tests with lower sensitivity than NAATs (e.g., culture), and therefore may have underestimated treatment failure. Other limitations of prior chlamydia treatment studies included inability to limit repeat sexual exposure and nonadherence with the multi-dose doxycycline regimen. The possibility of higher treatment failure rates was supported by: 1) high observed chlamydia recurrence rates [6-9] (around 20% a few months post-therapy), which may represent treatment failure or repeat acquisition of chlamydia; 2) an *in vitro* study reporting differences in chlamydia eradication based on whether chlamydia is in an acute or persistent state, with doxycycline more effective against the former and azithromycin against the latter;[10] and 3) a study utilizing chlamydia NAATs demonstrating repeat chlamydia rates of 8% at 10-18 weeks following azithromycin treatment in women who denied interval sexual activity.[11]

Chlamydia prevalence is high in male and female adolescents,[12] especially those entering YCFs, where it has been reported in about 3-9% of males and 12-25% of females.[13-15] Long-term gender-segregated YCFs (usual continuous stay >4 weeks) are an ideal setting to study the true efficacy of chlamydia treatment because: 1) this population has a high chlamydia prevalence; 2) recurrent or new chlamydia can be excluded (due to the institutionalized setting without the ability to leave the facility unsupervised and that all participants residing in the facility

can be tested and treated at study initiation, minimizing exposure or re-exposure to other infected persons; see Section 4 for more detailed information on furloughs); and 3) nonadherence to chlamydia treatment can be limited as study medications can be given as directly observed therapy. Genotyping of the *C. trachomatis* major outer membrane protein (OmpA) is an additional tool that can be useful in confirming treatment failure. In the clinical setting of a gender-segregated YCF and in the absence of exposure to the original infecting partner, the finding of identical *ompA* sequences of the chlamydial strains from the screening visit and the repeat chlamydia-positive follow-up visit essentially confirms treatment failure (it would be very unlikely that the participant would be exposed to a new partner with the identical *ompA* sequence and there is expected to be no variation in the sequence of a participant's initial and follow-up *C. trachomatis* isolate with treatment failure).

Determining the true efficacy of chlamydia treatment regimens and whether a repeat positive chlamydia test post-therapy represents chlamydia treatment failure or recurrence is a public health priority. Considering the high rate of repeat chlamydia test positivity following therapy, the *in vitro* data suggesting differences in azithromycin versus doxycycline anti-chlamydia activity, and clinical data suggesting chlamydia treatment failure in women denying post-therapy sexual activity, we conducted a single center, phase III randomized treatment trial of CDC-recommended azithromycin versus doxycycline regimens for chlamydia in males and females residing in long-term YCFs in Los Angeles County.[16] Our study design was able to address major limitations of prior chlamydia treatment trials of azithromycin versus doxycycline. Of 567 participants enrolled December 2009 through April 2014, 284 were randomized to azithromycin and 283 to doxycycline. After accounting for early discontinuation before first follow-up at Day 28, 155 (55%) participants in each arm completed first follow-up and comprised the per protocol population (65% male and 35% female). The final study visit was completed May 2014. There were no treatment failures in the doxycycline arm. In the azithromycin arm, treatment failure occurred in five participants (3.2%; 95% CI: 0.4-7.4%). The observed failure rate difference in the treatments was 3.2%, with a 90% upper CI of 5.9%, exceeding the predetermined 5% cutoff for establishing azithromycin noninferiority. Treatment safety was also evaluated. Gastrointestinal symptoms were the most common adverse events (AEs) in each treatment arm, reported in <10%. No severe or serious AEs occurred, and no participants were discontinued due to an AE.

The trial was not designed or powered to evaluate azithromycin efficacy in symptomatic chlamydia-infected males. However, in a subanalysis of 102 males receiving azithromycin, there was a higher frequency of treatment failure in those who reported painful urination compared with those who did not (2 of 20 [10.0%] vs. 2 of 82 [2.4%], P=0.172).[16]

2.2 Rationale

The proposed study is designed to determine the frequency of chlamydia treatment failure in males treated with azithromycin who do versus do not have urethral symptoms. Azithromycin is FDA approved for use in the U.S. and remains CDC recommended for urogenital chlamydia treatment (irrespective of urethral symptoms).[4] As discussed above, a subanalysis from the

urogenital chlamydia treatment trial performed in YCFs suggested that the azithromycin treatment failure rate may be higher in males with urethral symptoms. Also, during the conduct of the trial, there were two nongonococcal urethritis (NGU) treatment trials that reported low azithromycin cure rates (77% and 86%) in men with symptomatic chlamydia urethritis.[17,18] Taken together, these studies and the recent subanalysis suggest that azithromycin for treatment of chlamydia in males with urethral symptoms deserves further study.

Prior chlamydia treatment studies evaluating azithromycin had one or more major limitations: 1) not being able to exclude re-infection or new infection as an explanation for a repeat positive chlamydia test post-therapy; 2) not being able to ensure azithromycin is successfully re-dosed in those who vomit within one hour of azithromycin administration; and 3) not always confirming the chlamydial infection is present at the time the treatment is initiated (some infections may have already resolved when patients return for treatment of a positive screening chlamydia test). Our study addresses these limitations through: 1) use of a study population where repeat infection from an untreated partner is very unlikely (a gender-segregated YCF population where subjects are screened and treated for chlamydia upon entry into the facility); 2) repeating chlamydial testing at the time treatment is initiated to ensure chlamydial infection is still present; 3) performing *C. trachomatis* OmpA genotyping on chlamydia strains in those with repeat infections to exclude new infection (and to confirm treatment failure with the same strain); and 4) administration of azithromycin as directly observed therapy and then re-dosing the medication if vomiting occurs within one hour of initial administration. In addition to evaluating the azithromycin treatment failure rate in males based on presence of urethral symptoms, this study will also investigate whether the enrollment *C. trachomatis* OmpA genotype and median organism load are associated with treatment failure.

We hypothesize that the chlamydia treatment failure rate following azithromycin 1 gm administration will be significantly higher in males reporting urethral symptoms at the time of treatment. We also hypothesize that: 1) the enrollment OmpA genotype will not be associated with treatment failure, and 2) however a higher enrollment *C. trachomatis* organism load will be associated with a higher treatment failure rate.

Because study participant accrual rates at a single Los Angeles (LA) County YCF are too small to permit timely answers to the pressing question of frequency of chlamydia treatment failure in males following azithromycin administration, we propose to enroll at multiple YCFs in the LA County Correctional System, as was done for the prior clinical trial, to address our hypotheses. Facilities may be central detention centers, camps and/or placements that are part of the LA County YCF system.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Azithromycin is FDA approved and is a first line recommended antibiotic for chlamydial infection treatment. In addition, azithromycin has been in use for many years with an excellent safety

profile. The major side effects are gastrointestinal, with nausea, vomiting, abdominal cramping, and diarrhea possible. On rare occasions, severe hypersensitivity allergic reactions to azithromycin, erythromycin, macrolide and ketolide drugs have been reported. Because azithromycin is principally eliminated via the liver, caution is recommended when azithromycin is administered to patients with impaired hepatic function (reference: package insert). We do not foresee any psychological, social, legal, economic, or any other risks to subjects.

2.3.2 Known Potential Benefits

Treatment of chlamydia may prevent complications in males (e.g., epididymitis and infertility) and transmission to others. This study may improve our understanding of the efficacy of azithromycin for treatment of uncomplicated urogenital chlamydia in males based on whether they have urethral symptoms. It may also provide insight into other factors influencing chlamydia treatment success.

3 OBJECTIVES

3.1 Study Objectives

- The primary objective of this study is to:

  Assess the microbiological efficacy of azithromycin in uncomplicated *Chlamydia trachomatis* infection in males with versus without urethral symptoms in YCFs; in essence, this study will assess the frequency of chlamydia treatment failure to azithromycin at the Day 28 follow-up visit (Visit 2) in males with urethral symptoms compared to males without urethral symptoms.

- The secondary objectives of this study is to:

  Evaluate the association of laboratory findings (enrollment chlamydia load and OmpA genotype) and other participant characteristics (demographics, sexual behaviors, etc.) to chlamydia treatment failure in males after azithromycin treatment.

3.2 Study Outcome Measures

3.2.1 Primary Outcome Measures

Day 28 Follow-up (Visit 2):

Microbiological Cure:

Aptima Combo 2® Assay (AC2) (Hologic, Inc., San Diego, CA, USA) is negative for *C. trachomatis* at the Day 28 follow-up visit (Visit 2).

Microbiological Failure:

AC2 is positive for *C. trachomatis* at the Day 28 follow-up visit (Visit 2) and *C. trachomatis* OmpA genotyping reveals the baseline chlamydial strain and the repeat positive chlamydial strain to have the same *ompA* sequence (i.e., concordant).

If a participant has discordant *ompA* sequences and no evidence for mixed strain infection, they will be classified as a new infection and not considered a microbiological failure.

OmpA genotyping is not successfully performed on the baseline or repeat positive chlamydial isolate (i.e., there is an insufficient number of *ompA* copies in the sample to successfully amplify), but the participant did not have an unsupervised furlough (i.e., a leave from the YCF) prior to the chlamydia testing and the participant denies sexual activity with another person in the interval between treatment and repeat testing.

Unevaluable:

Participant did not return for chlamydia testing at the Day 28 follow-up visit (Visit 2) or could not be tested for any reason at the Day 28 follow-up visit (Visit 2); this includes participants who are withdrawn from the study due to an AE or epididymitis.

Participant had an AC2 negative for *C. trachomatis* at the time treatment was initiated (enrollment visit).

Participant vomits the single dose of azithromycin within one hour of administration and is not successfully re-dosed with azithromycin within 24 hours of the initial treatment.

Participant did not complete therapy.

Participant has an unsupervised furlough.

Indeterminate Outcome:

C. trachomatis OmpA genotyping cannot be successfully performed on the repeat chlamydial isolate and the participant reports sexual exposure in the interval between treatment and repeat testing or the participant had an unsupervised furlough prior to the chlamydia test. These participants will be excluded from the primary analysis.

3.2.2 Secondary Outcome Measures

The study will evaluate whether demographical characteristics (collected at baseline) and clinical parameters (collected at baseline and follow-up visits) predict treatment outcome (treatment success versus failure). In addition to the more extensive STD clinical parameter assessment that occurs at baseline, clinical parameters will be recorded for all participants at each follow-up visit.

4 STUDY DESIGN

The proposed study is a single center (with multiple long-term YCFs) treatment trial of the CDC-recommended azithromycin regimen (1 gm PO once) for chlamydia in males residing in long-term gender-segregated YCFs. This study is designed primarily to determine the frequency of chlamydia treatment failure following azithromycin in males who do versus do not have urethral symptoms of urethral discharge and/or dysuria.

Males age 12-21 years in good health (based on vital signs and provider's clinical evaluation documented in medical records) who are residing in long-term gender-segregated (not co-ed) YCFs (usual stay >3 weeks) and who are identified as chlamydia-infected comprise the study population. Only individuals who have a positive chlamydia screening test (i.e., any currently approved *C. trachomatis* NAAT) are enrolled, and those with negative screening tests are excluded. Detention facilities categorized as adult detention facilities or those with inmates older than age 21 are not appropriate for this protocol. Participants who have gonorrhea co-infection or evidence of epididymitis are excluded. Participants known to be HIV-positive will not be excluded as there are no data to support differences in efficacy of chlamydia treatment if co-infected. HIV testing or knowledge of a participant's HIV status is not required in our protocol but will be noted if known.

Consenting chlamydia-positive participants at the enrollment visit (Visit 1) will be enrolled, asked to provide demographic data, to provide a first-catch urine sample (not a mid-stream specimen) for repeat chlamydia and gonorrhea testing with AC2, and then will be treated with azithromycin 1 gm PO single dose given as directly observed. If a participant's AC2 from the enrollment treatment visit returns negative for *C. trachomatis,* they will be removed from the study. Participants whose AC2 at the enrollment treatment visit is positive for *C. trachomatis* will then be asked to provide a first-catch urine sample for repeat chlamydia testing with AC2 at 28 days after study drug initiation (i.e., Day 28 follow-up visit, (Visit 2)).

Furloughs will usually be supervised by a chaperone (e.g., adult YCF staff), although there may be furloughs where there is a brief period without supervision. For each participant enrolled, the date of any furloughs will be documented, and it will also be recorded: 1) whether they were supervised versus having a period of time without supervision; and 2) who served as the supervisor. In the event that a participant temporarily leaves the YCF (furlough) and is not supervised by a custody staff chaperone at all times, they will be excluded from the trial.

For the enrollment and the Day 28 follow-up visit (Visit 2), all participating YCFs will use AC2 for chlamydia testing. In addition, two aliquots of each enrollment and follow-up visit urine sample will be initially stored at 0-10° C for OmpA genotyping and measurement of organism load at University of Alabama at Birmingham (UAB). All specimens will be shipped to UAB on ice packs. Aliquots from urine samples that test positive for *C. trachomatis* will undergo OmpA genotyping and organism load measurement. Aliquots from urine specimens that test negative for *C. trachomatis* will be discarded upon receipt at UAB. Participants undergo an interview at

the enrollment and follow-up visit. Participants who test chlamydia-positive at the follow-up visit will be treated and followed per their clinical provider's routine standard of care.

Study participation is voluntary. Chlamydia-positive participants choosing not to participate in the study will receive treatment per their clinical provider's routine standard of care. Participants who test positive for *N. gonorrhoeae* or have a clinical diagnosis of epididymitis at enrollment will be removed from the study and excluded from analysis. Because participants reside in a YCF, they are not allowed to receive monetary or other direct benefits at any study visit.

The study will be monitored by a data safety monitoring board.

5 STUDY ENROLLMENT AND WITHDRAWAL

Participants will be recruited and followed in long-term YCFs located in Los Angeles County. After participants are identified as having urogenital chlamydia through screening with a *C. trachomatis* NAAT at each YCF, they will be approached about potential participation in the study. The study will enroll up to 446 males until complete data are obtained on at least 357 evaluable participants who are assessed at the Day 28 follow-up visit (Visit 2). Offer of enrollment will be limited to those who are in custody at the time of receipt of their initial positive CT test results and who have court ordered detention in youth camp or have tested positive for CT and are likely to remain in custody through treatment and through at least the Day 28 follow-up visit (Visit 2). Study retention will be improved by inclusion of those subjects with an anticipated length of stay at a participating YCF of at least 28 days.

As the study population is comprised of adolescents and prisoners, additional protections pertaining to these populations will be assured according to Institutional Review Board (IRB) and Office for Human Research Protections (OHRP) regulations.

5.1 Subject Inclusion Criteria

Participants must meet all of the following inclusion criteria in order to be eligible to participate in the study:

1. Male between the ages of 12 and 21 years
2. Residing in a long-term gender-segregated (no co-ed) YCF
3. Diagnosed with urogenital chlamydia as determined by a screening *C. trachomatis* NAAT
4. Anticipated length of stay at the YCF at the time of enrollment is at least 28 days
5. Willingness to provide written consent
6. Willingness to comply with study procedures

5.2 Subject Exclusion Criteria

Participants meeting any of the following criteria will be excluded from study participation:

1. Diagnosed with gonorrhea as determined by a screening *Neisseria gonorrhoeae* NAAT
2. Clinical diagnosis of epididymitis based on review of medical records
3. Known allergy to azithromycin, erythromycin, any macrolide or ketolide drug

4. History of liver problems due to use of azithromycin

5. Having received antimicrobial therapy with activity against *C. trachomatis* within 21 days of the positive chlamydia screening NAAT or in the interval between the positive screening NAAT and study enrollment

6. Any concomitant infection, which requires antimicrobial therapy with activity against *C. trachomatis*

7. Previously enrolled in this study

8. Unable to swallow pills

9. Other exclusion criteria, per clinician judgment, that prohibits subject from enrolling in study

5.3 Withdrawal Procedures

5.3.1 Reasons for Withdrawal

Participants are free to withdraw from participating in the study at any time upon request for any reason.

A study participant will be discontinued from participation in the study if:

1. The participant requests termination of participation.

2. Any clinical AE or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.

3. The participant tests positive for *C. trachomatis* prior to enrollment, but tests negative for *C. trachomatis* by repeat AC2 test administered at the enrollment visit after receiving study medication.

4. The participant has an unsupervised furlough after receiving the study medication.

5. The participant permanently leaves the LA County YCF system prior to completing the Day 28 follow-up visit (Visit 2).

6. The participant is clinically diagnosed with epididymitis during or following enrollment.

7. The participant received any antimicrobial therapy with activity against *C. trachomatis* other than the study medication between enrollment and the Day 28 follow-up visit (Visit 2).

8. The participant is unable to swallow the study medication and there is not an acceptable alternative formulation (i.e. suspension).

9. A medical condition develops, which in the judgment of the investigator requires that the participant be discontinued from further study participation.

10. The participant vomits within one hour of azithromycin re-administration.

5.3.2 Handling of Withdrawals

If participants are discontinued from study participation due to an AE or serious adverse event (SAE), including development of epididymitis, then they will be given appropriate care and treatment under medical supervision until the condition has resolved or becomes stable. Safety data will be collected on any participant who is discontinued from the study because of an AE (as specified in Section 9.2.1), SAE or epididymitis.

If study personnel learn that a participant is still infected upon release from the LA County YCF system, study personnel will refer them on for further treatment according to their clinical provider's routine standard of care. Participants who are withdrawn due to permanently leaving the LA County YCF system before the Day 28 follow-up visit (Visit 2) but who completed their study medication regimen and tolerated without difficulty will not be contacted for repeat chlamydia testing ("test of cure" is not routine practice in participants with uncomplicated chlamydia who complete their treatment). Participants withdrawn due to detection of gonorrhea will be treated with a CDC recommended antibiotic regimen.

5.3.3 Termination of Study

There are no anticipated reasons for early termination of the study. This study may be terminated by the DMID Sexually Transmitted Infections (STI) Branch at any time.

6 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1 Study Product Description

6.1.1 Acquisition

Azithromycin is FDA approved for use in the U.S. Azithromycin 500 mg tablets will be purchased through the University of Southern California (USC) and will only be used for investigational purposes.

6.1.2 Formulation, Packaging, and Labeling

Azithromycin will be supplied as 500 mg film-coated tablets for oral administration. They will be packaged and distributed in routine pharmaceutical bottles, packets, foils, or similar appropriate containers. Any medication that is distributed to a study participant will be provided by authorized site staff associated with the study. Medication will be placed into appropriate packaging with a label that clearly outlines the dose, dosing schedule, and number of pills to take.

6.1.3 Product Storage and Stability

Azithromycin is stable at room temperature and will be stored at 15-30° C (59-86° F).

6.2 Dosage, Preparation and Administration of Study Intervention/Investigational Product

A licensed, registered Site Research Pharmacist may be delegated the responsibility of study product dispensation. If a Research Pharmacist is not available, a physician, nurse practitioner, physician assistant, registered nurse, or other authorized healthcare practitioner, who is a member of the clinical study staff, may be delegated to dispense the study product. These personnel must be licensed, trained, and must be authorized to dispense the study product under state and local rules and regulations.

Azithromycin will be directly administered orally and can be taken with or without food, but may be tolerated better with food. Dosage and preparation will be as follows:

- Azithromycin – A 1 gm single dose is directly administered to participants by authorized site staff associated with the study on Day 1. This dose is comprised of two 500 mg tablets. A single repeat dose of azithromycin will be allowed if first dose of azithromycin is vomited within 1 hour of ingestion.

6.3 Modification of Study Intervention/Investigational Product for a Subject

There will be no modifications of the study medication.

6.4 Accountability Procedures for the Study Intervention/Investigational Product(s)

The Site Investigator (SI) is responsible for the distribution and disposition of study product, and has ultimate responsibility for accountability. The SI may delegate to the site Research Pharmacist or designee (e.g., Study Coordinator (SC)) responsibility for study product accountability. This designee will be responsible for maintaining complete records and documentation of study product receipt, accountability, dispensation, storage conditions, and final disposition of the study product. All study products, whether administered or not, must be documented on the appropriate study product accountability record or dispensing log.

Used and unused study product will be retained until monitored and released for disposition, as applicable. Upon completion or termination of the study and after the final monitoring visit, any remaining unused study product will either be returned or destroyed appropriately at the clinical site as per Sponsor requirements and instructions.

Azithromycin study tablets will be kept in a locked, temperature-controlled storage cabinet at USC until transferred to participating YCFs, according to site-approved product transportation standard operating procedures (SOPs). The designee will maintain a master product accountability log, which will document the receipt of study product from the pharmacy and distribution to each participating YCF. Azithromycin study tablets will be stored at the YCFs in controlled rooms with limited and secured access only to nurses and approved staff and will be segregated from other clinic medication. The study product will be administered by the authorized site staff associated with the study. At each YCF, a product accountability log will be completed by authorized staff associated with the study and will document receipt of study product from USC, dispensation to study participants, and final disposition. The SC will be responsible for reconciliation between the master and YCF product accountability logs. All study accountability logs will include documentation of the antibiotic's lot number, expiration date, manufacturer name, and storage information.

6.5 Assessment of Subject Compliance with Study Intervention/Investigational Product

All azithromycin 1 gm regimens will be given and directly observed by authorized site staff associated with the study and recorded in the participants' clinic and study chart.

6.6 Concomitant Medications/Treatments

In the event of an AE or SAE while in the study, concomitant medications (other than antacids co-administered with the study medication or antimicrobial therapy with activity against *C. trachomatis*) may be administered as necessary to manage the event. Participants may also take any concomitant medication during the study (other than antimicrobial therapy with activity against *C. trachomatis*) for other medical (e.g., asthma, etc.) or psychiatric (e.g. depression, etc.) conditions. If the participant vomits within one hour of azithromycin re-administration, they will be withdrawn from the study and will be treated per routine standard of care.

7 STUDY SCHEDULE

Schedule of study visits:

Visit 1 – Enrollment

Visit 2 – Day 28 after study drug initiation

7.1 Screening

Male adolescents at participating long-term gender-segregated YCFs receive routine clinical sexually transmitted disease (STD) education and screening for chlamydia and gonorrhea by NAAT. Subjects whose chlamydia screening test is positive will be approached by the study site personnel for determination of interest in participating in the study and to ensure potential participants meet all inclusion and exclusion criteria.

7.2 Enrollment (Visit 1)

At enrollment (Visit 1), the study personnel will confirm the participant's positive chlamydia screening test and will review inclusion and exclusion criteria to confirm eligibility.

At each YCF, study-trained personnel will conduct the IC process.

After consent is obtained, demographic information, medical history and sexual history will be collected. Participants will be asked to provide a first-catch urine specimen (approximately 20-30 ml) for repeat chlamydia and gonorrhea testing by AC2. Participants who have voided within the past hour will be asked to wait or return for urine collection one or more hours since the last void. Two aliquots of the urine sample will be stored at 0-10° C until shipped to UAB for OmpA genotyping and measurement of organism load. All specimens will be shipped to UAB. Aliquots from urine samples that test positive for *C. trachomatis* will undergo OmpA genotyping and organism load measurement. Aliquots from urine specimens that test negative for *C. trachomatis* will be discarded upon receipt at UAB.

After urine collection is complete, azithromycin 1 gm will be administered to each participant per protocol. The participant will be observed taking the study medication and the date and time documented. Each participant who has not eaten within the previous 1-2 hours will be offered a small snack prior to taking any study medication dose to improve tolerability. A single repeat dose of azithromycin will be allowed if the first dose of azithromycin is vomited within 1 hour of ingestion. If the participant vomits within 1 hour of re-administration, they will be withdrawn from the study and will be treated per routine standard of care.

The urine specimen aliquoted for AC2 testing will be processed as described in Section 8.2.1, labeled with the study number, participant number, visit number, and date and time of collection, and sent to the Los Angeles County Department of Public Health (LACDPH) laboratory for

testing. The two urine samples aliquoted for OmpA genotyping and organism load determination will be refrigerated at the LACDPH laboratory at 0-10° C until shipped to UAB where CT-negative specimens will be discarded upon receipt.

Participants will receive counseling on sexual abstinence during the study.

7.3 Follow-up Visit (Visit 2)

Prior to this visit, the study site personnel will review results of the AC2 from the enrollment visit and confirm the test was positive for *C. trachomatis*. Those participants with AC2 negative for *C. trachomatis* at the enrollment visit are removed from the study and will not participate in the follow-up visit. Participants who remain eligible will be asked to provide a first-catch urine specimen (approximately 20-30 ml) for chlamydia testing by AC2 at 28 days following initiation of the study drug regimen. Two aliquots of the urine sample will be stored at 0-10° C until shipped to UAB for OmpA genotyping and measurement of organism load. All specimens will be shipped to UAB. Aliquots from urine samples that test positive for *C. trachomatis* will undergo OmpA genotyping and organism load measurement. Aliquots from urine specimens that test negative for *C. trachomatis* will be discarded upon receipt at UAB.

Participants will be queried regarding any possible side effects of the study medication. Participants undergo a brief assessment on clinical parameters since enrollment. Per Section 3.1, the primary objective of the study is assessment of treatment outcome at the Day 28 follow-up visit (Visit 2). The study will enroll up to 446 males until complete data are obtained on at least 357 evaluable participants who are assessed at the Day 28 follow-up visit (Visit 2). Participants will be evaluated for the treatment outcome at Visit 2 according to the following definitions:

Microbiological Cure (treatment success):

AC2 is negative for *C. trachomatis* at the Day 28 follow-up visit (Visit 2).

Microbiological Failure (treatment failure):

- AC2 is positive for *C. trachomatis* at the Day 28 follow-up visit (Visit 2) and *C. trachomatis* OmpA genotyping reveals the baseline chlamydial strain and the repeat positive chlamydial strain to have the same *ompA* sequence (i.e., concordant).

- If a participant has discordant *ompA* sequences and no evidence for mixed strain infection, they will be classified as a new infection and not considered a microbiological failure.

- OmpA genotyping is not successfully performed on the baseline or repeat positive chlamydial isolate (i.e., there is an insufficient number of *ompA* copies in the sample to successfully amplify), but the participant did not have an unsupervised furlough (i.e., a

leave from the YCF) prior to the chlamydia testing and the participant denies sexual activity with another person in the interval between treatment and repeat testing.

8 STUDY PROCEDURES/EVALUATIONS

8.1 Clinical Evaluations

- Prior to enrollment, results and date of the screening chlamydia and gonorrhea test (part of juvenile intake procedure) will be obtained by study site personnel. Only those with a positive chlamydia test and negative gonorrhea test will be approached for possible enrollment.

- After consent is obtained, additional eligibility criteria will be determined. This includes assessing if participant has received antimicrobial therapy with activity against *C. trachomatis* within 21 days of positive chlamydia screening NAAT (or in the interval between the positive screening NAAT and study enrollment) and whether participant has epididymitis symptoms based on medical records. If a participant is noted to have received antimicrobial therapy with activity against *C. trachomatis* usage within 21 days of screening or has had a clinical diagnosis of epididymitis between screening and enrollment, then the participant is ineligible.

- Eligible participants will be enrolled and demographic information (race, ethnicity and date of birth), STD history, and sexual history will be recorded onto a data collection form at the enrollment visit.

- At the end of the enrollment visit, azithromycin 1 gm is administered to each participant and ingestion is directly observed and time of administration recorded.

- At the enrollment visit, counseling will be given regarding the importance of sexual abstinence during the course of the study.

- Prior to the follow-up visit, AC2 test results from the enrollment visit are reviewed to ensure continued eligibility.

- At follow-up visit, medical history including epididymitis symptoms, sexual history including sexual activity, information on furloughs, defined AEs (see Section 9.2.1), and SAEs are recorded. Results of AC2 testing at each visit are reviewed when they become available and are used for classification of treatment outcomes for that visit.

8.2 Laboratory Evaluations

8.2.1 Clinical Laboratory Evaluations

Specimens for evaluation are first-catch urine specimens (approximately 20-30 ml) collected at enrollment and the follow-up visit (Visit 2) and aliquoted as follows:

- One urine specimen for AC2 testing which will be performed per the manufacturer's instructionsat the LACDPH laboratory.

- Two urine specimens for OmpA genotyping and measurement of organism load will be refrigerated at LACDPH laboratory at 0-10° C until shipped to UAB. All specimens will be shipped to UAB. Aliquots from urine specimens that test positive for *C. trachomatis* will undergo OmpA genotyping and measurement of organism load. Aliquots from urine specimens that test negative for *C. trachomatis* will be discarded upon receipt at UAB.

8.2.2 Special Assays or Procedures

C. trachomatis OmpA genotyping will be performed on urine specimens at UAB in Dr. Geisler's laboratory under his direct supervision by previously reported methodology.[19] CT organism load quantification will also be performed on stored urine specimens at Dr. Barbara Van Der Pol's laboratory at UAB using real-time PCR (Cobas® 4800, Roche, Indianapolis, IN, USA). To estimate organism load, a *C. trachomatis* calibrator is run using stock *C. trachomatis* samples with known organism counts to create cycle threshold standard curves for comparison with clinical samples, providing reliable and reproducible results that allow for relative quantification on a log scale.

8.2.3 Specimen Preparation, Handling, Storage and Shipment

8.2.3.1 Instructions for Specimen Preparation, Handling, and Storage

Urine specimens should be immediately aliquoted, refrigerated and delivered to the LACDPH laboratory per routine courier pick-up schedule. All specimens are to be labeled with the study number, participant number, visit number, and date and time of collection. At the LACDPH laboratory, AC2 testing will be done per manufacturer's instructions. The two specimens for OmpA genotyping and measurement of organism load will be refrigerated at 0-10° C until shipment to UAB.

8.2.3.2 Specimen Shipment

Urine specimens will be shipped on ice packs Monday through Wednesday with overnight delivery to the following laboratory address:

LaDraka' Brown
University of Alabama at Birmingham
703 19th St South, 242 Zeigler Research Building
Birmingham, AL 35294-0007
(205) 996-5382 (phone)
(205) 975-7764 (fax)

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

The primary safety concern of this study is gastrointestinal tolerability of the azithromycin regimen, which is the most common AE associated with azithromycin and was the most common reported by males in the prior chlamydia treatment trial conducted in the same study population.[16] Because safety of azithromycin was one of the study objectives of the previous chlamydia treatment trial and because no subjects receiving azithromycin withdrew due to an AE or experienced an SAE,[16] we will not evaluate all AEs as an objective of the current study. However, because gastrointestinal tolerability of azithromycin could influence our efficacy outcome, we will collect data on reported gastrointestinal symptoms. We will also collect data on any SAE.

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

9.2.1 Adverse Events

Gastrointestinal AEs that occur after study drug administration (Visit 1) and through the Day 28 follow-up visit (Visit 2) will be recorded on an AE case report form (CRF). AEs which cause a participant to discontinue from the study after study drug administration (Visit 1) and through the Day 28 follow-up visit (Visit 2) will be recorded on an AE CRF.

At the follow-up visit (Visit 2), subjects will be queried regarding the occurrence of any gastrointestinal side effects since enrollment visit, and any such AEs will be recorded in the subject's research chart and periodically monitored by the SI.

Adverse Event: An AE is defined as any untoward medical occurrence in a study subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the study antibiotic regimens. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

AEs related to gastrointestinal reactions, including those not meeting the criteria for SAEs, should be captured on the Adverse Event CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis, which would include MD, PA, Nurse Practitioner, DO, or DDS), and time of resolution/stabilization of the event. AEs must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Pre-existing gastrointestinal conditions should be noted at baseline and not reported as an AE. However, if it deteriorates on or before the Day 28 follow-up visit (Visit 2), it should be recorded as an AE.

All AEs, as specified in Section 9.2.1, must be graded for severity and relationship to study product.

FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Severity of Event: The following guidelines will be used to quantify intensity:

Gastrointestinal side effects which include nausea, vomiting, abdominal pain, and diarrhea will be assessed on a scale of 1 to 3 according to the toxicology table in Appendix B of this protocol.

Other AEs will be graded using the following general criteria:

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

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

Relationship to Study Products: The SI's or provider's assessment of an AE's relationship to test article (study drug) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study product assessed using the terms: related or not related. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- Related – There is a reasonable possibility that the study product caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the AE.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

9.2.2 Serious Adverse Events

An adverse event 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 during the period of protocol defined surveillance
- Life Threatening adverse event (defined as a subject at immediate risk of death at the time of the event)
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance
- Results in a persistent or significant disability/incapacity.
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. 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.

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

All positive tests for gonorrhea and chlamydia will be reported within 24 hours to the appropriate study personnel by the LACDPH laboratory. In the event of a positive test for gonorrhea, study personnel will contact the subject to arrange for treatment and discontinuation from the study. Test results will be reported by name to the LA County health department as required by law.

9.3 Reporting Procedures

All AEs specified in Section 9.2.1 including local and systemic reactions not meeting the criteria for “serious adverse events” will be captured on Adverse Event CRF. Information to be collected includes event description, time of onset, investigator assessment of severity, relationship to study product, and time of resolution/stabilization of the event. Adverse events must be documented appropriately regardless of relationship.

As noted in Section 9.2.1, medical conditions that are present at the time the subject is screened should be considered as baseline and not reported as an AE.

All Sexually Transmitted Infection Clinical Trials Group (STI CTG) protocols follow the NIAID guidelines for reporting of AEs. The FHI 360 Center for Data Management (CDM) will provide a listing of AEs to the Principal Investigator (PI) for review on a monthly basis. The CDM will

compile these events in a secure tabular format and forward them to the Protocol Specialist (PS) for posting on the study's SharePoint site within the STI CTG. The Protocol Team has access to the specific study SharePoint.

All serious adverse events will be immediately reported to the SI at each site and to the PI, Dr. Geisler. In addition, SAEs should be reported to all pertinent IRBs according to their AE reporting guidelines. The CDM, the DMID Clinical Project Manager (CPM), and the PS should be notified within 24 hours.

All AEs that meet the expedited reporting requirements of NIAID are reported to DMID's pharmacovigilance contractor. These events will be referred to as SAEs. DMID's pharmacovigilance contractor will respond to SAEs and will disseminate reports to the DMID Medical Monitor, the PI, and the PS. It is the responsibility of each YCF to provide this information to the LA County IRB, if required.

9.3.1 Serious Adverse Events

All SAEs will be:

- recorded on the appropriate SAE form
- followed through resolution by a study physician
- reviewed by a study physician

SAEs must be documented from the first study intervention, Study Day 1 through the Day 28 follow-up visit.

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

Medical Affairs/Pharmacovigilance
DMID Pharmacovigilance Group
Clinical Research Operations and Management Support (CROMS)
6500 Rock Spring Dr. Suite 650
Bethesda, MD 20814, USA
SAE Hot Line: 1-800-537-9979 (US)
SAE FAX Phone Number: 1-800-275-7619 (US)
SAE Email Address: PVG@dmidcroms.com

Questions about SAE reporting can be referred to the SAE Hotline (available 24 hours a day/7 days a week)

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

The DMID medical monitor and CPM will be notified of the SAE by the DMID Pharmacovigilance Group. The DMID medical monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct.

At any time after completion of the study, if the investigator becomes aware of an SAE that is suspected to be related to study product, the investigator will report the event to the DMID Pharmacovigilance Group.

Plans for Assuring Compliance with Requirements Regarding the Reporting of Adverse Events (AE)

- The SC will transmit copies of all SAEs (including deaths) within the timeframes specified above. These events will be entered into an SAE database on a protocol-specific basis.
- Tabulations of SAEs will be electronically transmitted quarterly to NIAID/DMID with hard copies to the PI and to the NIAID Project Officer and to the NIAID Medical Monitor. These tabulations will consist of cumulative summaries of SAEs by type of event, severity grade, and relationship to study drug therapy.
- Sign-off by the NIAID Medical Monitor, PI, and NIAID Project Officer within 5 working days of receipt and returned to complete tracking process.

Plans for Assuring that any Action Resulting in a Temporary or Permanent Suspension of an NIAID-funded Clinical Trial is Reported to the NIAID Program Director Responsible for the Contract

In the event that termination of the trial or major modification to the protocol is under consideration, the PI will convene the protocol team and SI by conference call to discuss the options. The STI CTG Coordinating Center will inform the NIAID Program Director when studies are temporarily or permanently closed. All amendments to protocols must be approved by the NIAID.

9.3.2 Regulatory Reporting for Studies Not Conducted Under DMID-Sponsored IND

As this study will not be conducted under an Investigational New Drug Application (IND), MedWatch will be used to report related AEs. DMID will be copied simultaneously when an alternate method of reporting is utilized.

9.3.3 Other Adverse Events

Not applicable.

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

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

9.5 Halting Rules

Findings that will alert the PI to conduct a safety review will include the number of SAEs overall, the number of occurrences of a particular type of SAE, and severe AEs/reactions. If the PI and the NIH Medical Monitor determine that the number of SAEs and severe AEs/reactions warrants investigation, the PI will immediately request that enrollment be halted until such an investigation has been completed. The study enrollment and dosing will be halted for Data and Safety Monitoring Board (DSMB) review if two study subjects develop the same study product related SAE.

9.6 Safety Oversight

DATA AND SAFETY MONITORING PLAN

The proposed research does not include any IND or Investigational Device Exemption (IDE). All study procedures will be approved by IRBs at each institution, and the site will notify IRBs, according to their guidelines, of any AEs that could possibly be attributed to participation in the study.

A DSMB will be created to review this study. The DSMB will be approved by the DMID. Meetings of the DSMB will be arranged, facilitated, and documented by CROMS SOCS. The initial responsibility of the DSMB will be to approve the initiation of this clinical trial. After this approval and annually during the course of the trial, the DSMB responsibilities are to:

- Review the research protocol, IC documents, and plans for data and safety monitoring;
- Evaluate the progress of the trial, including periodic assessments of data quality and timeliness, subject recruitment, accrual and retention, subject risk versus benefit,
- Performance of the trial site, and other factors that can affect study outcome;
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the subjects or the ethics of the trial;
- Review clinical centers performance, make recommendations and assist in the resolution of problems reported by the PI;

- Protect the safety of the study subjects;
- Report on the safety and progress of the trial;
- Review SAEs for increased frequency, although SAEs are not anticipated for this trial;
- Make recommendations to the sponsor, the PI, and if required, to the FDA concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- Ensure the confidentiality of the trial data and the results of monitoring;
- Assist the PI by commenting on any problems with study conduct, enrollment, and sample size and/or data collection.

Members will likely include experts in STDs, clinical trials methodology, and biostatistics. Members will consist of persons independent of the investigators who have no financial, scientific, or other conflict of interest with the trial. Written documentation attesting to absence of conflict of interest will be required.

The first meeting, also known as the organizational meeting, will take place before initiation of the study to discuss the protocol, approve the commencement of the study, and to establish the charter to monitor the study. The DSMB will meet annually. A final DSMB meeting will take place at the close-out of the study. An ad hoc emergency meeting of the DSMB can be called at any time by any party should question of subject safety arise. The PI and the SI and/or other study team members will be present (via conference call) at each meeting. A simple majority will be considered a quorum for DSMB meeting and voting purposes. The DSMB will advise DMID of its findings.

10 CLINICAL MONITORING

10.1 Site Monitoring Plan

DMID, the sponsoring agency, or its designee will conduct site-monitoring visits as detailed in the clinical monitoring plan and in accordance with DMID policies. Site monitoring is conducted to ensure that the human subject protections, study and laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, ICH/GCP guidelines and applicable regulations; and that the study is conducted in accordance with the protocol, protocol-specific manual of procedures and applicable sponsor SOPs. Monitoring visits will include, but are not limited to, inspection of study facilities, review of regulatory files, accountability records, CRFs, informed consent forms (ICFs), printouts of medical and laboratory reports from the electronic medical records (EMR) system, and protocol and GCP compliance. Site monitors will have access to the study site, study personnel, and all study documentation according to the DMID-approved site monitoring plan. Study monitors will meet with SIs to discuss any problems and actions to be taken and document visit findings and discussions.

Site visits will be made at standard intervals as defined by DMID and may be made more frequently as directed by DMID. Following a monitoring visit the monitors will disseminate a report to the study site, the PI, CDM, CPM, and the PS.

11 STATISTICAL CONSIDERATIONS

11.1 Study Hypotheses

The primary objective of this study is to determine whether there is a significant difference in the urogenital chlamydia treatment failure rate in males treated with azithromycin 1 gm who do versus do not have urethral symptoms. We hypothesize that the chlamydia treatment failure rate will be significantly higher in males with urethral symptoms compared with no symptoms at the time of azithromycin treatment. The primary endpoint, treatment failure, will be evaluated at the Day 28 follow-up visit (Visit 2). As a secondary endpoint, treatment failure will be evaluated based on treatment outcome assessed at the Day 28 follow-up visit (Visit 2) and all non-study visits. Secondary objectives of the study are to determine whether the enrollment OmpA genotype and the enrollment *C. trachomatis* organism load are associated with treatment failure.

We hypothesize that OmpA genotype will not be associated with treatment failure, however there will be a significantly higher median *C. trachomatis* organism load in those with treatment failure compared to the median load in those without treatment failure.

11.2 Sample Size Considerations

The primary outcome measure is chlamydia treatment failure, and the primary endpoint is occurrence of treatment failure at the Day 28 follow-up visit (Visit 2, see Section 3.2.1). The sample size calculation is based on data extrapolated from the recent analysis of the NIAID sponsored trial since the study would be extended in the same clinical setting and with similar clinical procedures. Of the factors that may influence the azithromycin treatment rate, presence of urethral symptoms is the primary one of interest based on preliminary findings from the initial RCT and findings from the two recent NGU studies. [17,18] Assumptions are that 20% of enrolled chlamydia-infected males will have urethral symptoms and azithromycin treatment failures will occur in 10% of symptomatic men vs. 2% of asymptomatic men. To detect a significant difference at the one-sided 0.05 significance level with power of 0.80 will require a sample size of 357 evaluable males, approximately 72 symptomatic and 285 asymptomatic males. Assuming 20% of males enrolled will be unevaluable for azithromycin treatment failure (either due to leaving the YCF before the Day 28 test-of-cure follow-up visit (Visit 2) or due to having a negative enrollment CT test), a total of 446 males will need to be enrolled. In accordance with ICH Statistical Guidelines, a one-sided significance level is used for testing.

11.3 Planned Interim Analyses (if applicable)

11.3.1 Safety Review

The DSMB will receive an annual safety report, prepared by the study statistician with input from the PI, with each scheduled DSMB meeting. Because AEs are expected to be uncommon and

mostly of mild severity, we have not identified any specific safety criteria for stopping the study due to adverse events. Indeed, possible minor side effect of treatment will be monitored as one of the study outcomes. However, the DSMB will be independent of study investigators and will be able to make recommendations based on the data it receives. In addition, the DSMB will receive immediate notification of any SAE that could be related to the study. The DSMB will decide whether to halt enrollment.

The null hypothesis is that the treatment failure rate at the Day 28 follow-up visit (Visit 2) is 10% for males with urethral symptoms (discharge and/or dysuria) versus 2% for males without urethral symptoms. After half of the study participants have Day 28 follow-up visit (Visit 2) outcome data available, an interim analysis will be performed.

The DSMB will receive an independent presentation of interim results, prepared by the study statistician. In preparation for each annual DSMB meeting, we will prepare summary reports of recruitment (by site), known outcome events, and any adverse events (including medication side effects). In addition, one interim analysis of the primary efficacy outcomes will occur when half of subjects have Day 28 follow-up visit (Visit 2) outcome data available using the Lan-DeMets spending function with an O'Brien-Fleming boundary for the values of the boundaries and the associated operating characteristics) to maintain the overall significance level of 0.05 for the primary outcome analysis, and to assess the significance of the interim results that emerge during the trial. The purpose of the interim analysis is to determine whether a difference in efficacy between symptomatic and asymptomatic participants can be established early before all participants are enrolled and complete follow-up.

Information Rate	Reject H_0 (one-sided)	P-value
0.50	Z > 2.538	0.006
1.00	Z > 1.662	0.05

11.4 Analysis Population

The primary analysis population for treatment failure will be the per protocol population, which is comprised of subjects who complete therapy and whose failure status can be established at the Day 28 follow-up visit (Visit 2). See Section 3.2.1 for definitions of evaluable subjects for the per protocol population.

11.5 Final Analysis Plan

For each of the two groups of males (those with versus without urethral symptoms), the binomial proportion and its 95% confidence interval will be used to estimate the failure rate. The Mantel-Haenszel-Cochran test will be used to compare the two groups across YCFs with respect to failure rate. To evaluate racial and ethnic group variation with respect to failure rate, a logistic

regression analysis will be performed with failure rate as the outcome variable, and with symptom status (symptomatic, asymptomatic), race and ethnicity included as covariates. While the primary analysis will use the combined urethral symptom variable (discharge and/or dysuria), secondary analyses with each urethral symptom will also be performed.

An ordinal scale will be used to quantify the intensity of each AE (0-None, 1-Mild, 2-Moderate, and 3-Severe). The incidence and severity level of AEs will be summarized for all subjects for each visit.

To assess the association between clinical/laboratory parameters and chlamydia treatment failure, including OmpA genotype and *C. trachomatis* organism load, univariate analyses of each factor against treatment failure will be conducted using Fisher's exact test for dichotomous factors and the Wilcoxon rank sum test for continuous variables. Those which are statistically significant at the 0.10 level will be incorporated into a logistic regression model. Since the underlying treatment failure rate is expected to be 0.04 (approximately 13 of 357 evaluable subjects), it may be difficult to identify characteristics that are associated with failure rate.

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The site will maintain appropriate medical and research records for this study, in compliance with ICH E6 GCP, Section 4.9 and regulatory and site institutional requirements for the protection of confidentiality of subjects. Only the named investigator(s) and research personnel assigned to the project will have access to the records. As part of participating in a DMID-sponsored study, the site will permit authorized representatives of DMID, and the FDA to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

All facilities of Los Angeles County Juvenile Probation are included in a "closed" system. EMRs can be accessed from all facilities within the system and are available when minors are transferred to a different facility. All medical records are stored electronically in a secure database. Only authorized staff have access to individual medical records of minors. Medical records for persons in the study will be marked indicating they are participating in a study.

Study specific lab results and certified copies obtained from medical records should not contain personal identifying information. All study participants will receive a unique participant number that will be recorded on all paper forms. Paper CRFs, consent forms, contact information sheets, and other paper data collection instruments will be stored in a locked file cabinet located in a secure location at the study site. In addition, all CRFs will be entered into the primary data entry and management system at FHI 360 CDM. Only approved site study staff, monitors, the FDA and auditors will access these files.

13 QUALITY CONTROL AND QUALITY ASSURANCE

Following a written DMID-accepted site quality management plan, the participating site is responsible for conducting routine quality assurance (QA) and quality control (QC) activities to internally monitor study progress and protocol compliance. The study site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

FHI 360 CDM, the data-coordinating center for this STI CTG study, will implement quality control procedures beginning with the data entry system. All data collected for the trial will be thoroughly checked for accuracy, completeness, and adherence to this protocol and GCP. Specifically, CDM staff review, double data verification, the DMNet web portal quality control tools, and SAS programs check study data and CRFs for errors in procedure and data entry, missing and out of range data, and consistency within and across forms. All discrepant data will be queried and all discrepancies will be sent to the site for resolution on a regularly scheduled basis. Further detail on data quality control can be found in Section 15 of this protocol.

All staff participating in the study will have received appropriate training in ethical issues involving human subject protection and good clinical practice, as required by NIH and their local institutions. Training documentation will be kept current and will be maintained on site.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Ethical Standard

This study will be conducted in full conformity with the Declaration of Helsinki, with the International Conference for Harmonization Good Clinical Practice (ICH-GCP) regulations and guidelines, or with the Office of Human Research Protection guidelines involving prisoners in Research, whichever affords the greater protection to the subject.

The investigator will also ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

14.2 Institutional Review Board

Prior to the enrollment of participants into this trial, the approved protocol and ICF will be reviewed and approved by the appropriate ethics review committee or IRB. The responsible official for the IRB will sign the IRB letter of approval prior to the start of the trial and a copy will be provided to DMID. Any amendments to the protocol or consent materials will also be approved by the IRB before they are implemented.

All participating institutions hold a current U. S. Federal-Wide Assurance issued by OHRP. The IRB Federal Wide Assurance number will be provided to DMID.

Each participating YCF shall comply with all requirements for approval or notification of research to be conducted. Research conducted in Los Angeles County shall comply with the legal authority that governs the conduct of research within the YCF as specified by the *Superior Court, Juvenile Division, Chapter 7*, available at http://www.lacourt.org/courtrules/ui/index.aspx?ch=Chap7&ct=TR&tab=2. As required, upon final local IRB approval, a petition to the *Superior Court, Juvenile Division* must also be submitted and approved.

14.3 Informed Consent Process

A written and signed ICF will be obtained from each participant prior to enrollment. The participant will be asked to read the consent or may request to have the consent read to him. Upon reviewing the consent with the participant, the site study staff will explain the research study and answer any questions that may arise. The participants will have the opportunity to discuss the study prior to agreeing to participate. The participants will sign the ICF prior to any procedures being done specifically for the study.

The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed ICF will be offered to the participants. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. Decisions regarding a participant's stay at the YCFs will not be adversely affected if a participant declines to participate in this study.

14.3.1 Informed Consent Process (in Case of a Minor)

Due to the nature of this research, IRB approval will be sought to enroll minors aged 12 to 17 years old with a waiver of parental consent. California statute grants minors, ages 12 years or older, the right to consent to the diagnosis and treatment of any suspected sexual transmitted disease without parental notification or specific parental consent as specified under *Family Code 6926 (a)* [http://law.onecle.com/california/family/6926.html]. Hence, to require parental consent to participate in this research study would result in the unintended consequence of a violation of the confidentiality protections currently guaranteed to minors under existing laws.

Since azithromycin is considered a currently accepted first line treatment for chlamydia, as recommended in the CDC treatment guidelines, we are requesting that a waiver of parental consent to participate in research be granted. Azithromycin is the treatment currently being routinely used in this setting for chlamydia treatment (primarily due to the single dose treatment option). This study population, which has high chlamydia rates and a study setting which makes re-infection unlikely for a sufficiently long time period after treatment to assess treatment efficacy, provides a unique opportunity to address an important medical and public health matter that would otherwise not be possible to study.

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

Per Section 2.1 and 2.2 discussion, only males are enrolled in this study. The demographic and ethnic distribution of the study population will be generally reflective of the distribution of STDs within the county of each gender-segregated YCF. No male will be excluded based on their demographic or ethnic status. The study will include children, adolescents, and adults ages 12 to 21, which is also an age group with the highest rates of chlamydia.

14.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data and all other information generated will be held in strict confidence. In the event that a participant reports sexual assault, sexual abuse, or non-consensual sex during the course of data collection, staff will follow standard reporting procedures within the juvenile correctional system. No information concerning the study or the

data will be released to any unauthorized third party, without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the Investigator for the participants in this study, including printouts of relevant source documentation from the site's EMR system. The clinical study site will permit access to such records.

Additional precautions will be taken to ensure subject confidentiality, including keeping contact information separate from data, using secure computer systems with upgraded virus software, keeping study files in locked cabinets, and confirming the identify of persons who are contacted over the telephone.

14.6 Study Discontinuation

In the event that the study is discontinued, participants will be notified. Participants will be given appropriate care and treatment for chlamydia under medical supervision until the condition has resolved or becomes stable.

15 DATA HANDLING AND RECORD KEEPING

The CDM at FHI 360 serves as the data coordinating center for this STI CTG study. The CDM will provide assistance with all aspects of data management which will be carried out in accordance with GCP, this protocol, and relevant FHI 360 SOPs.

The PI will work closely with the CDM and will oversee all aspects of data management.

15.1 Data Management Responsibilities

A detailed data management (DM) plan will be written prior to study initiation. It will be modified during the study when significant changes are made to document how data are handled in the study. The following is a brief summary of the plan.

The CDM will format the CRFs based on the content development by the PI. The data manager will obtain final approval for the CRFs from the PI and PS. The CDM will produce, distribute, maintain, and implement version control for all study CRFs.

All study participants will be assigned a unique participant identifier that will be required on all CRFs, study collection instruments, and files used in analysis. Instructions for assigning site and participant numbers will be in the DM plan.

The CDM will design a study-specific 21 CFR Part 11 compliant clinical database. Error specifications will be written in consultation with the statistician to check for accuracy, completeness, and consistency on the CRFs. The error specifications will be run regularly and will produce ‘discrepancies’ that will be sent to the site electronically.

Data will be entered and verified through double data entry. Illegible, out-of-range, or other data that cannot be entered will be flagged and sent to site study staff for clarification.

The CDM will provide reports on study progress and will provide in-house and medical coding using the most current version of the dictionary of Medical Dictionary for Regulatory Activities (MedDRA), specified in the DM plan. All coding will be reviewed by the PI.

Data freezes will be requested by the statistician for all interim and final reports. Thorough cleaning and closure of participant data will be performed at study close-out according to the DM plan. Prior to closure all participant data will be complete or accounted for.

15.2 Data Capture Methods

All data will be recorded on CRFs supplied by FHI 360 CDM. Each CRF must be initialed and dated by the on-site study staff member who completed it. The SI, however, is responsible for the accuracy of data entered on the CRFs and will sign a statement on the final form for each

participant stating that he or she has reviewed all CRFs for that participant and certifies that all information on them is correct.

The source documents including signed ICFs, laboratory reports, patient records, and the CRFs should be maintained in the participant's file, and should be available for review during monitoring visits.

The completed CRFs will be emailed to CDM. The original CRFs will be retained at the site in the participant's clinic study file. It is imperative that the original and emailed copies match in every detail. Therefore no changes may be made on the originals or the emailed copies after the CRFs have been submitted to CDM. Before the CRFs are submitted, any change to the data should be dated and initialed by the person making the change. Use of opaque correction fluid is not permitted. Changes needed after the original has been emailed must be documented with requests for Manual Data Discrepancies.

All CRFs should be stored securely. File cabinets should be locked, maintained, and viewed by study staff only. No names or personal identifying information will be contained on the CRFs. Access to all CRFs will be restricted to authorized personnel.

CRFs that have been emailed to CDM will be filed in participant file folders, ordered by participant number, in a file cabinet or drawer designated for the study. These CRFs are stored in a locked file room at CDM.

Data will be double-entered by trained data entry staff at the CDM. All data will be stored in FHI 360 CDM's 21 CFR Part 11 compliant clinical database.

Error specifications will be developed to check data for accuracy and completeness. All discrepancies with the error specifications will be sent to the site using an Internet-based system, which allows for electronic communication between site staff and CDM staff. FHI 360 CDM staff will update the database based on the SI's or designee's written response. SIs or designees must keep copies of all discrepancies stapled to the CRFs in the participant's study file.

15.3 Types of Data

Data for this study includes clinical (e.g., epididymitis) and microbiological (e.g., chlamydia test results, OmpA genotypes, *C. trachomatis* organism load) outcomes, demographic (e.g., age and race/ethnicity) and clinical parameters (relating to sexual history taken in participants with treatment failure), as well as safety data for participants who have been discontinued from the study due to an AE or epididymitis.

15.4 Timing/Reports

The CDM will generate monthly and quarterly reports that provide information on data submissions, data quality, and information that might be helpful in making operational decisions.

The contents and frequency of these reports will be based on the PI's requests. A detailed description of the regular data reports will be provided in the DM plan, which will be finalized before the start of data collection. Ad hoc reports will also be generated as needs arise.

FHI 360 CDM will produce data freezes for the study based on requests from the project leader, statistician or PS. Data will be uploaded to a secure web-portal and access to download these data will be granted via login and password to individuals listing in the request for a data freeze.

15.5 Study Records Retention

Hard copies of all CRF emails and data discrepancy forms will be kept at FHI 360 CDM for a minimum of three years after study completion. Records may not be destroyed without written permission from NIAID/DMID.

Study sites will maintain study records and reports, including, but not limited to, CRFs, source documents, ICFs, laboratory test results, and medication inventory records for 3 years after study completion. The investigator may transfer custody of the records to another person who will accept responsibility for them. Notice of transfer must be given to the sponsor preferably before, but no more than ten days after the transfer.

No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the investigator and FHI 360 CDM when these documents no longer need to be retained.

15.6 Protocol Deviations

A protocol deviation (PD) is any noncompliance with the clinical trial protocol or GCP. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed though a plan agreed upon by the site and the study PI and then implemented promptly.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within five working days of identification of the PD, or within five working days of the scheduled Protocol-required activity. All deviations will be promptly reported to DMID, via DMID-designated contractor's web- or fax-based system.

All deviations from the Protocol will be addressed in study subject source documents. A completed copy of the DMID PD Form will be maintained in the Regulatory File, as well as in the subject's study chart. PDs will be sent to the local IRB/Independent Ethics Committee (IEC) per their guidelines. The SI and study personnel are responsible for knowing and adhering to their IRB requirements.

16 PUBLICATION POLICY

Following completion of the study, the investigator is expected to publish the results of this research in a scientific journal. The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov[20], which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. It is the responsibility of DMID to register this trial in an acceptable registry. Any clinical trial starting enrollment after 01 July 2005 must be registered on or before patient enrollment.

The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (e.g., Phase I trials), would be exempt from this policy.

Any presentation, abstract, or manuscript will be made available by the Investigator to the STI CTG Manuscript Review Committee and DMID for review prior to submission or presentation.

17 LITERATURE REFERENCES

1. World Health Organization. Global incidence and prevalence of selected curable sexually transmitted infections – 2008. http://www.who.int/reproductivehealth/publications/rtis/2008_STI_estimates.pdf (accessed November 23, 2015).
2. Cates W. Estimates of the incidence and prevalence of sexually transmitted diseases in the United States. Sex Transm Dis. 1999;26:S2-7.
3. Farley TA, Cohen DA, Elkins W. Asymptomatic sexually transmitted diseases: the case for screening. Prev Med 2003;36:502–9.
4. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines 2015. MMWR Recomm Rep 2015;64:1-137
5. Lau C, Qureshi AK. Azithromycin verus doxycyline for genital chlamydial infections. Sex Transm Dis. 2002;29:497-502.
6. Xu F, Schillinger JA, Markowitz LE, et al. Repeat *Chlamydia trachomatis* infection in women: analysis through a surveillance case registry in Washington State, 1993-1998. Am J Epidemiol. 2000;152:1164-70.
7. Kjaer HO, Dimcevski G, Hoff G, et al. Recurrence of urogenital *Chlamydia trachomatis* infection evaluated by mailed samples obtained at home: 24 weeks' prospective follow up study. Sex Transm Infect. 2000;76:169-72.
8. Whittington WL, Kent C, Kissinger P, et al. Determinants of persistent and recurrent *Chlamydia trachomatis* infection in young women: results of a multicenter cohort study. Sex Transm Dis. 2001;28:117-23.
9. Burstein GR, Snyder MH, Conley D, et al. Adolescent chlamydia testing practices and diagnosed infections in a large managed care organization. Sex Transm Dis. 2001;28:477-83.
10. Reveneau N, Crane DD, Fischer E, Caldwell HD. Bactericidal activity of first-choice antibiotics against gamma interferon-induced persistent infection of human epithelial cells by *Chlamydia trachomatis*. Antimicrob Agents Chemother. 2005;49:1787-93.
11. Golden MR, Whittington WLH, Handsfield HH, et al. Impact of expedited sex partner treatment on recurrent or persistent gonorrhea or chlamydial infection. N Eng J Med. 2005;352:676-85.
12. Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2014.* Atlanta: U.S. Department of Health and Human Services; 2015.
13. Mertz KJ, Voigt RA, Hutchins K, et al. Findings from STD screening of adolescents and adults entering correctional facilities. Sex Transm Dis. 2002;29:834-9.
14. Bauer HM, Chartier M, Kessell E, et al. Chlamydia screening of youth and young adults in non-clinical settings throughout California. Sex Transm Dis. 2004;31:409-14.
15. Robertson AA, Thomas CB, St. Lawrence JS, Pack R. Predictors of Infection with chlamydia or gonorrhea in incarcerated adolescents. Sex Transm Dis. 2005;32:115-22.

16. Geisler WM, Uniyal A, Lee JY, Lensing SY, Johnson S, Perry RCW, Kadrnka CM, Kerndt PR. Azithromycin versus Doxycycline for Urogenital *Chlamydia trachomatis* Infection. N Eng J Med. 2015;373:2512-21.
17. Schwebke JR, Rompalo A, Taylor S, Seña AC, Martin DH, Lopez LM, Lensing S, Lee JY. Re-evaluating the treatment of nongonococcal urethritis: emphasizing emerging pathogens--a randomized clinical trial. Clin Infect Dis. 2011 Jan15;52(2):163-70.
18. Manhart LE, Gillespie CW, Lowens MS, Khosropour CM, Colombara DV, Golden MR, Hakhu NR, Thomas KK, Hughes JP, Jensen NL, Totten PA. Standard treatment regimens for nongonococcal urethritis have similar but declining cure rates: a randomized controlled trial. Clin Infect Dis. 2013 Apr;56(7):934-42.
19. Geisler WM, Black CM, Bandea CI, Morrison SG. *Chlamydia trachomatis* OmpA genotyping as a tool for studying the natural history of genital chlamydial infection. Sex Transm Inf 2008;84:541-544.
20. De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. N Engl J Med. 2004;351:1250-1.

SUPPLEMENTS/APPENDICES

APPENDIX A: SCHEDULE OF EVENTS

Procedures	Visit 1 (Enrollment)	Visit 2 (Day 28)
Written Consent	X	
Assessment of Eligibility Criteria	X	
Review Relevant Medical History	X	X
Review Sexual History/Activity	X	X
Review Demographic Information	X	
Counseling on Sexual Abstinence During the Trial	X	
Confirmation of Positive Chlamydia	X	
Assessment of Clinical Parameters		X
Completion of CRFs	X	X
Review of Concomitant Medications	X	X
Review of Concomitant Immunizations	X	X
Administration of Study Medication	X	
Assessment of Adverse Events	(X)	X
Laboratory: • First-Catch Urine for AC2 • CT load determination and CT OmpA genotyping	 X (X)	 X (X)

At enrollment, all procedures should be done before study intervention.
(X) indicates events that occur as needed.

APPENDIX B: TOXICOLOGY TABLES

	Grade 1	Grade 2	Grade 3
Nausea	No interference with activity	Some interference with activity	Prevents daily activities
Vomiting	No interference with activity or 1 - 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity or requires IV hydration
Diarrhea	2 - 3 loose or watery stools or < 400 gms/24 hours	4 - 5 loose or watery stools or 400 - 800 gms/24 hours	6 or more loose or watery stools or > 800 gms/24 hours or requires IV hydration
Abdominal Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity