CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN

for

DMID Protocol: 15-0015

Study Title:

Phase IIa Randomized, Single-blinded, Placebo-controlled Clinical Trial of the Reprofiled Drug Auranofin for GI Protozoa

NCT02736968

Version 2.0

DATE: 29 APRIL 2020

STUDY TITLE: Phase IIa Randomized, Single-Blinded, Placebo-Controlled Clinical Trial of the Reprofiled Drug Auranofin for Gi Protozoa

Protocol Number Code:	**DMID Protocol: 15-0015**
Development Phase:	Phase IIa
Products:	Auranofin
Form/Route:	One dose (two capsules containing 3 mg each) per day orally of auranofin for seven days to treat amebiasis; one dose (two capsules containing 3 mg each) per day of auranofin for five days to treat giardiasis.
Indication Studied:	*Amebiasis and giardiasis*
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	
Clinical Trial Completion Date:	
Date of the Analysis Plan:	29 April 2020
Version Number:	**2.0**

This study was performed in compliance with Good Clinical Practice.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C	Celsius
CI	Confidence Interval
CRF	Case Report Form
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data and Safety Monitoring Board
EDC	Electronic Data Capture
ELISA	Enzyme-linked Immunosorbent Assay
ER	Emergency Room
F	Fahrenheit
GGT	Gamma Glutamyl Transferase
GMT	Geometric Mean Titer
GMFR	Geometric Mean Fold Rise
icddr,b	International Center for Diarrheal Disease Research, Bangladesh
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	Intention to Treat
L	Liter
LLN	Lower Limit of Normal
mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mEq	Milliequivalent
mg	Milligram
mITT	Modified Intention to Treat
mL	Milliliter
MAR	Missing at Random

List of Abbreviations *(continued)*

MCAR	Missing Completely at Random
MNAR	Missing Not at Random
N	Number (typically refers to subjects)
NIH	National Institutes of Health
PI	Principal Investigator
PP	Per Protocol
PT	Preferred Term
RBC	Red Blood Cell
RCD	Reverse Cumulative Distribution
SAE	Serious Adverse Event
SD	Standard Deviation
SDCC	Statistical and Data Coordinating Center
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard Operating Procedures
U	Units
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization

1. PREFACE

The Statistical Analysis Plan (SAP) for "Phase IIa Randomized, Single-blinded, Placebo-controlled Clinical Trial of the Reprofiled Drug Auranofin for GI Protozoa" (DMID Protocol 15-0015) describes and expands upon the statistical information presented in the protocol.

This document describes all planned analyses and provides reasons and justifications for these analyses. It also includes sample tables, listings, and figures planned for the final analyses. Regarding the final analyses and Clinical Study Report (CSR), this SAP follows the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, as indicated in Topic E3 (Structure and Content of Clinical Study Reports), and more generally is consistent with Topic E8 (General Considerations for Clinical Trials) and Topic E9 (Statistical Principles for Clinical Trials). The structure and content of the SAP provides sufficient detail to meet the requirements identified by the FDA and ICH, while all work planned and reported for this SAP will follow internationally accepted guidelines published by the American Statistical Association and the Royal Statistical Society for statistical practice.

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

2. INTRODUCTION

This study investigates the effectiveness of auranofin for two gastrointestinal protozoa: E. histolytica and Giardia. This proposed clinical trial follows from key findings in studies supported by U01 AI0778822 entitled, "Novel Therapeutics for Class B Protozoa," to design and develop highly effective antiparasitic agents for Class B Protozoa. The development of the first high-throughput whole cell screens for E. histolytica (Debnath, 2012) and G. lamblia (Gut et al., 2011) against FDA-approved drugs and bioactive compounds (a "repurposing" screen), found that auranofin had a ten-fold lower IC50 (0.5 μM) compared with metronidazole (5.2 μM) for E. histolytica and an equivalent IC50 for Giardia (4.0 μM). Auranofin is an orally available gold-containing compound that has been in clinical use in the treatment of rheumatoid arthritis for 25 years. As previous research has found auranofin to be the first drug active against Entamoeba and Giardia with a clearly defined target, the FDA has given auranofin Orphan Drug status.

This study is a Phase IIa clinical trial conducted in Bangladesh. The initial plan for this study included a single site, the International Center for Diarrheal Disease Research, Bangladesh (icddr,b). The study initially planned to enroll 136 males and non-pregnant females aged 18 to 65 years with asymptomatic amebiasis (68 subjects) or giardiasis (68 subjects). Participants within each disease group were to be randomized in a 1:1 ratio to receive auranofin or a placebo. The amebiasis group was to receive 6 mg auranofin (or placebo) daily for seven days while the giardiasis group was to receive 6 mg auranofin (or placebo) daily for five days. The initial primary goal of the study, reflected in versions 1 - 4 of the protocol, was to compare the proportion of subjects with parasitological response, defined as no detection of cysts or trophozoites on microscopic exam or negative antigen detection, between treatment arms by Day 7 for amebiasis and by Day 5 for giardiasis.

However, the protocol endpoints and study population were revised because after screening 2,396 people during 17 months with only 34 enrolling into the study, it became apparent that enrolling 136 asymptomatic subjects would be infeasible. For this reason, eligibility criteria were revised, starting with protocol version 5, to enroll symptomatic rather than asymptomatic adult patients (still with amebiasis or giardiasis). The goal, as before, was to enroll 68 in each disease group and randomize in a 1:1 ratio within each disease group to receive either auranofin or placebo. The dosing regimen was unchanged, but the primary outcome was revised for the new (symptomatic) study population. The new primary outcome is resolution of diarrhea (less than 3 loose stools / 24 hours) by Day 7 for the symptomatic amebiasis group and by Day 5 for the symptomatic giardiasis group. Furthermore, in version 7 of the protocol, a new site was also added (Rajshahi Medical College Hospital), after which randomization was stratified by site as well as disease group. The protocol revision specified that the asymptomatic and symptomatic subjects would be analyzed separately.

The study populations, study design, and primary outcome for each of these populations are summarized by protocol version in Table 1:

Table 1: Summary of Study Population, Study Design, and Primary Outcome by Protocol Version

Protocol Versions	Study Population	Target Sample Size	Treatment Allocation	Dosing Regimen	Primary Outcome
1-4	Asymptomatic amebiasis	68	1:1 (auranofin: placebo)	7 days	Parasitological response (no detection of cysts or trophozoites on microscopic exam or negative antigen detection) by Day 7
	Asymptomatic giardiasis	68	1:1 (auranofin: placebo)	5 days	Parasitological response (no detection of cysts or trophozoites on microscopic exam or negative antigen detection) by Day 5
5-7	Symptomatic amebiasis	68	1:1 (auranofin: placebo) [a]	7 days	Resolution of diarrhea (less than 3 loose stools / 24 hours) by Day 7
	Symptomatic giardiasis	68	1:1 (auranofin: placebo) [a]	5 days	Resolution of diarrhea (less than 3 loose stools / 24 hours) by Day 5

[a] Randomization was also stratified by site for subjects enrolled under protocol version 7 because a second site was added in that protocol version.

Secondary objectives for the asymptomatic population are summarized in Table 2, while those for the symptomatic population are summarized in Table 3. The changes in secondary outcomes for the symptomatic population are shown in blue in Table 3.

Table 2: Secondary Outcomes for the Asymptomatic Study Population

Outcome	Time points, Asymptomatic Amebiasis Group	Time points, Asymptomatic Giardiasis Group
Parasitological response (no detection of cysts or trophozoites on microscopic exam or negative antigen detection)	Days 3 and 5	Day 3
Rate of decrease in trophozoite/cyst load by qPCR in stools	Days 3, 5, and 7	Days 3 and 5
Negative stool antigen test	Days 3, 5, 7, and 14	N/A
Sustained cure (no detection of cysts or trophozoites by microscopic exam or negative antigen detection)	Days 14 and 28	Days 14 and 28
Relapse (same strain) or re-infection (new strain) with positive stools by genotyping the initial vs. subsequent strain.	Day 14 and/or 28	Day 14 and/or 28

Table 3: Secondary Outcomes for the Symptomatic Study Population

Changes to outcomes from the asymptomatic population are shown in blue:

Outcome	Time points, Symptomatic Amebiasis group	Time points, Symptomatic Giardiasis group
Parasitological response (no detection of trophozoites on microscopic exam [a])	Days 3, 5, and 7 [b]	Day 3 and 5 [b]
Rate of decrease in trophozoite/cyst load by qPCR in stools	Days 3, 5, and 7	Days 3 and 5
Negative stool antigen test	Days 3, 5, 7, and 14	Days 3 and 5
Sustained cure (no detection of trophozoites by microscopic exam) [c]	Days 14 and 28	Days 14 and 28
Relapse (same strain) or re-infection (new strain) with positive stools by genotyping the initial vs. subsequent strain.	Day 14 and/or 28	Day 14 and/or 28
Time to resolution of diarrhea [d]	Assessment over the study period	Assessment over the study period

[a] The definition of parasitological response was revised to allow for cysts and remove the antigen test.
[b] Moved from primary to secondary outcome.
[c] Modified so definition of "cure" matches the updated definition of parasitological response for this population.
[d] New outcome for this study population.

2.1. Purpose of the Analyses

The overall goal is to assess the safety and efficacy of auranofin compared to a placebo for the treatment of asymptomatic amebiasis and giardiasis among males and non-pregnant females aged 18-65 years old in Bangladesh in two study populations: asymptomatic and symptomatic.

Two analyses will be conducted – one for the asymptomatic patients and another for the symptomatic patients, each according to their corresponding outcome measures. This SAP includes analysis plans for both study populations.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

Auranofin is a "repurposed" drug with established pharmacology and is approved for human use by the FDA. This study assesses clinical efficacy for two new indications, amebiasis and giardiasis, with a randomized Phase IIa, placebo-controlled, single-blinded, superiority trial comparing auranofin for treatment of amebiasis and giardiasis to placebo. Parasite clearance will be analyzed in the asymptomatic population, while resolution of diarrhea will be studied in the symptomatic population. Ultimately, the goal will be to expand the trial to include symptomatic children after proving efficacy and safety in adults.

All subjects will have the same screening protocol, but the trial will evaluate subjects with amebiasis or giardiasis with separate primary and secondary endpoints. Below, objectives for the asymptomatic population are excerpted below from Version 4.0 of the Study Protocol, the first version under which participants were enrolled, and those for the symptomatic population are excerpted below from Version 7.0 of the Study Protocol.

3.1.1. Objectives for the Asymptomatic Population

Primary *E. histolytica*:

To compare the proportion of subjects with parasitological response (no detection of cysts or trophozoites of E. histolytica on microscopic exam or negative antigen detection) by Day 7

Secondary *E. histolytica*:

1. To compare the proportion of subjects with parasitological response (no detection of cysts or trophozoites on microscopic exam or negative antigen detection) by Day 3 and 5
2. To compare the rate of decrease in trophozoite/cyst load by qPCR in stools by Days 3, 5, and 7
3. To compare the proportion of subjects with negative stool antigen test by Days 3, 5, 7, and 14
4. To compare the proportion of subjects with sustained cure (no detection of cysts or trophozoites by microscopic exam or negative antigen detection) at 14 and 28 days
5. To compare the proportion of subjects with relapse (same strain) or re-infection (new strain) with positive stools at 14 and/or 28 days by genotyping the initial vs. subsequent strain

Primary *Giardia*:

To compare the proportion of subjects with parasitological response (no detection of cysts or trophozoites on microscopic exam or negative antigen detection) by Day 5

Secondary *Giardia:*

1. To compare the proportion of subjects with parasitological response (no detection of cysts or trophozoites on microscopic exam or negative antigen detection) by Day 3
2. To compare the rate of decrease in trophozoite/cyst load by qPCR in stools by Days 3 and 5
3. To compare the proportion of subjects with sustained cure (no detection of cysts or trophozoites by microscopic exam or negative antigen detection) at 14 and 28 days

4. To compare the proportion of subjects with relapse (same strain) or re-infection (new strain) with positive stools at 14 and/or 28 days by genotyping the initial vs. subsequent strain

3.1.2. Objectives for the Symptomatic Population

Primary *E. histolytica:*

To compare the proportion of subjects with stools positive by rapid EIA and positive antigen detection EIA for E. histolytica at enrollment with resolution of diarrhea (less than 3 loose stools/ 24 hours) by Day 7.

Secondary *E. histolytica:*

- To compare the proportion of subjects with positive rapid EIA and positive antigen detection EIA for *E. histolytica* and trophozoites on smear (wet mount or concentrated trichrome) at enrollment with parasitological response (no detection of trophozoites on microscopic exam) by Day 7.
- To compare the proportion of subjects with positive rapid EIA and positive antigen detection EIA for *E.* histolytica and trophozoites on smear at enrollment with parasitological response (no detection of trophozoites on microscopic exam) by Day 3 and 5.
- To compare the rate of decrease in trophozoite/cyst load by qPCR in stools by Days 3, 5, and 7.
- To compare the proportion of subjects with negative stool antigen test by Days 3, 5, 7, and 14.
- To compare the proportion of subjects with sustained cure (no detection of trophozoites by microscopic exam) at 14 and 28 days.
- To compare the proportion of subjects with relapse (same strain) or re-infection (new strain) with positive stools at 14 and/or 28 days by genotyping the initial vs. subsequent strain.
- To compare the time to resolution of diarrhea (less than 3 loose stools/24 hours)

Primary *Giardia:*

To compare the proportion of subjects with stool positive rapid EIA and positive antigen detection EIA for *Giardia* at enrollment with resolution of diarrhea (less than 3 loose stools/24 hours) by Day 5.

Secondary *Giardia:*

- To compare the proportion of subjects with parasitological response (no detection of trophozoites on microscopic exam) by Day 3 and 5.
- To compare the rate of decrease in trophozoite/cyst load by qPCR in stools by Days 3 and 5.
- To compare the proportion of subjects with negative stool antigens by days 3 and 5.
- To compare the proportion of subjects with sustained cure (no detection of trophozoites by microscopic exam) at 14 and 28 days.
- To compare the proportion of subjects with relapse (same strain) or re-infection (new strain) with positive stools at 14 and/or 28 days by genotyping the initial vs. subsequent strain.
- To compare the time to resolution of diarrhea (less than 3 loose stools/24 hours)

3.2. Endpoints

The asymptomatic endpoints are excerpted below from the Study Protocol, Version 4.0 (the first version under which participants were enrolled), and the symptomatic endpoints are excerpted from the Study Protocol, Version 7.0.

3.2.1. Asymptomatic Population Endpoints

Primary Outcome Measures

1. Proportion of subjects with parasitological response of *E. histolytica* (no detection of cysts or trophozoites of *E. histolytica* on microscopic exam or negative antigen detection) by Day 7.
2. Proportion of subjects with parasitological response of *Giardia* (no detection of cysts or trophozoites on microscopic exam or negative antigen detection) by Day 5

Secondary Outcome Measures

1. *E. histolytica:*
    a. Proportion of subjects with parasitological response (no detection of cysts or trophozoites on microscopic exam or negative antigen detection) by Day 3 and 5
    b. Rate of decrease of trophozoite/cyst load by qPCR in stools by Days 3, 5, and 7
    c. Proportion of subjects with negative stool antigen test by Days 3, 5, 7, and 14
    d. Proportion of subjects with sustained cure (no detection of cysts or trophozoites by microscopic exam or negative antigen detection) at 14 and 28 days
    e. Proportion of subjects with relapse (same strain) or re-infection (new strain) with positive stools at 14 and 28 days by genotyping the initial vs. subsequent strain
2. *Giardia:*
    a. Proportion of subjects with parasitological response (no detection of cysts or trophozoites on microscopic exam or negative antigen detection) by Day 3
    b. Rate of decrease of trophozoite/cyst load by qPCR in stools by Days 3 and 5
    c. Proportion of subjects with sustained cure (no detection of cysts or trophozoites by microscopic exam or negative antigen detection) at 14 and 28 days
    d. Proportion of subjects with relapse (same strain) or re-infection (new strain) with positive stools at 14 and 28 days by genotyping the initial vs. subsequent strain

3.2.2. Symptomatic Population Endpoints

Primary Outcome Measures

1. Proportion of subjects with positive rapid EIA and positive antigen detection EIA for *E.* histolytica and resolution of diarrhea (less than 3 loose stools/ 24 hours) by Day 7.
2. Proportion of subjects with positive rapid EIA and positive antigen detection EIA for *Giardia* and resolution of diarrhea (less than 3 loose stools/24 hours) by Day 5.

Secondary Outcome Measures

1. *E. histolytica:*

a. Proportion of subjects with positive rapid EIA and positive antigen detection EIA for *E. histolytica* and trophozoites on smear at enrollment with parasitological response (no detection of trophozoites on microscopic exam) by Day 7.
b. Proportion of subjects with positive rapid EIA and positive antigen detection EIA for *E.* histolytica and trophozoites on smear at enrollment with parasitological response (no detection of trophozoites on microscopic exam) by Day 3 and 5.
c. Rate of decrease of trophozoite/cyst load by qPCR in stools by Days 3, 5, and 7
d. Proportion of subjects with negative stool antigen test by Days 3, 5, 7, and 14
e. Proportion of subjects with sustained cure (no detection of trophozoites by microscopic exam) at 14 and 28 days
f. Proportion of subjects with relapse (same strain) or re-infection (new strain) with positive stools at 14 and 28 days by genotyping the initial vs. subsequent strain
g. Time to resolution of diarrhea (less than 3 loose stools/24 hours)

2. *Giardia:*

a. Proportion of subjects with positive rapid EIA and positive antigen detection EIA for *Giardia* and trophozoites on smear at enrollment with parasitological response (no detection of trophozoites on microscopic exam) by Day 3 and 5
b. Rate of decrease of trophozoite/cyst load by qPCR in stools by Days 3 and 5
c. Proportion of subjects with negative stool antigens by days 3 and 5.
d. Proportion of subjects with sustained cure (no detection of trophozoites by microscopic exam) at 14 and 28 days
e. Proportion of subjects with relapse (same strain) or re-infection (new strain) with positive stools at 14 and 28 days by genotyping the initial vs. subsequent strain
f. Time to resolution of diarrhea (less than 3 loose stools/24 hours)

3.3. Study Definitions and Derived Variables

For the purposes of enrollment into the asymptomatic population, potential subjects are ***diagnosed with amebiasis or giardiasis*** if they have a positive TechLab antigen test, positive wet mount or trichome, and positive stool PCR for *E. histolytica* or *Giardia*. In order to enroll, the subject must receive the diagnosis of amebiasis or giardiasis within 72 hours of enrollment. If a subject is infected with both *E. histolytica* and Giardia, they will be enrolled in the *E. histolytica* study arm. Once the *E. histolytica* study arm is fully enrolled, any subsequent dual infected subjects will be enrolled in the *Giardia* arm.

For enrollment into the symptomatic population, potential subjects are ***diagnosed with amebiasis or giardiasis*** if they have a positive rapid EIA and positive antigen detection EIA of *E. histolytica* or *Giardia*. These subjects must also have diarrhea (3 or more loose stools within 24 hours of enrollment). In order to enroll, the subject must receive the diagnosis of amebiasis or giardiasis within 4 days prior to enrollment. If a subject is infected with both *E. histolytica* and *Giardia*, they will be enrolled in the *E. histolytica* study arm. Once the *E. histolytica* study arm is fully enrolled, any subsequent dual infected subjects will be enrolled in the *Giardia* arm. If a subject is infected with both *Giardia* and *Cryptosporidium*, they will not be enrolled.

Parasitological response is defined as no detection of cysts or trophozoites on microscopic exam or negative antigen detection, for the asymptomatic population. Both tests will be performed on each subject. For the symptomatic population, however, ***parasitological response*** is defined as no detection of trophozoites on microscopic exam. The microscopic exam may include both wet mount and trichrome staining. If both were performed, then both must be negative for the microscopic exam to be negative.

Sustained cure on Day 14 is defined, for the asymptomatic amebiasis group, to be no detection of cysts or trophozoites on microscopic exam or negative antigen detection on Day 7 and again on Day 14. ***Sustained cure on Day 14*** is defined, for the symptomatic amebiasis group, to be no detection of trophozoites on microscopic exam on Day 7 and again on Day 14. ***Sustained cure on Day 14*** is defined analogously for the giardiasis groups but is based on measurements taken on Day 5 and 14.

Sustained cure on Day 28 is defined for the asymptomatic amebiasis group to be no detection of cysts or trophozoites on microscopic exam or negative antigen detection on Days 7, 14, and 28 (if specimens are obtained at each time point). ***Sustained cure on Day 28*** is defined for the symptomatic amebiasis group to be no detection of trophozoites on microscopic exam on Days 7, 14, and 28 (if specimens are obtained at each time point). It is defined analogously for the giardiasis groups but is based on measurements taken on Day 5, 14, and 28.

Relapse at Day X is defined as having a positive stool PCR at day X that is identified via genotyping to be identical to the strain of the original infection.

Reinfection at Day X is defined as having a positive stool PCR at day X that is identified via genotyping to be non-identical to the strain of the original infection.

In the two above definitions, the ***original infection*** is defined to be the strain of parasite measured in the stool sample collected on Visit 01.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This 28-day, Phase IIa, two-arm, randomized, placebo-controlled, single-blinded, superiority treatment study in 136 males and non-pregnant females ≥ 18 to 65 years of age was designed to compare placebo to once daily doses of auranofin (Ridaura) for adults with asymptomatic amebiasis (68 subjects) or giardiasis (68 subjects). Potential adult subjects who are otherwise healthy from the single site of the Mirpur community of Bangladesh were chosen from a randomized census list for a visit by a health professional from icddr,b. Once eligibility and consent were confirmed, subjects were stratified by infection (a 2-level variable of either amebiasis vs. giardiasis), and then within each stratum, randomized 1:1 to receive auranofin or placebo.

Because of difficulties in enrolling the target number of participants under the original design, the eligibility criteria were revised to study symptomatic rather than asymptomatic participants, beginning with protocol version 5. The new goal is to enroll a total of 136 symptomatic participants (68 in each disease group), in addition to the asymptomatic participants. The asymptomatic participants who enrolled under protocol versions 1-4 will be analyzed separately. In addition, a new site was added in protocol version 7.

Both study populations (asymptomatic and symptomatic) have the same dosing regimen. Subjects in the amebiasis group receive 6 mg auranofin or placebo delivered orally on Days 1, 2, 3, 4, 5, 6, and 7; those in the giardiasis group receive 6 mg auranofin or placebo orally on Days 1, 2, 3, 4, and 5. For both study populations, follow-up visits are conducted on dosing days, as well as on Day 7, 14, and 28. For the symptomatic population only, any subject with worsening diarrhea as assessed by the study physician, may have their dose discontinued and receive standard of care metronidazole. In this population, subjects who remain stool positive for giardiasis or amebiasis on the Day 28 visit will have a Day 30 visit to receive the standard of care treatment for giardiasis or amebiasis.

The placebo capsules are similar, but not identical to the study drug, so this study is considered single-blind. The laboratory personnel performing evaluations are blinded to treatment assignment. Subjects, investigators, and study personnel performing any study-related assessments following study product administration are not to be informed of group allocation, but could detect differences in study and placebo capsules. They were instructed to perform their clinical or AE assessments as though blinded to prevent potential bias.

The planned duration of subject participation for the asymptomatic population was 42 days of face to face visits, including the pre-enrollment screening period of 14 days. For the symptomatic population, it is 34 days of visits, including the pre-enrollment screening period of 4 days. It is anticipated that it will take approximately 3.5 years to finish the study. The Data Safety Monitoring Board (DSMB) meets at least annually to review safety data. Study enrollment will be stopped for DSMB review of safety data when the study reaches 50% enrollment (i.e. 68 subjects enrolled). DSMB will review safety data after the 68th subject completes visit 8. Data review for efficacy will be performed at the completion of enrollment. The final review meeting will occur 6 to 8 months after clinical database lock to review the cumulative unblinded safety and efficacy data for the study.

The schematics in Figure 1 and Figure 2 visualize the study schedule for the symptomatic population. The study schedule for the asymptomatic population is the same except that it excludes the Day 30 visit and has four screening visits instead of two.

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

This study compares auranofin (6 mg daily) given for 7 days to subjects infected with amebiasis or 5 days for those infected with giardiasis, to a placebo.

The study is single-blind because the auranofin capsules are similar, but not identical, to the placebo capsules. Each auranofin dose is comprised of two capsules, each containing 3 mg of white crystalline powder. Each capsule has an opaque brown cap and opaque tan body and is imprinted with the produce name RIDAURA. The placebo capsules are similar to auranofin capsules with opaque brown caps and an opaque tan body but are not imprinted with the product name RIDAURA. Since the treatment and placebo capsules are not identical, patients and staff dispensing medication are not considered blind. The subjects, investigators, and study personnel performing any study-related assessments following study product administration are not to be informed of group allocation but could detect differences in study and placebo capsules. They were instructed to perform their clinical or AE assessments as though blinded to prevent potential bias. However, the laboratory personnel performing evaluations are blinded to treatment assignment.

The selected dose of 6 mg per day of auranofin is the standard maintenance dose for rheumatoid arthritis. In the case of rheumatoid arthritis, auranofin may be prescribed for many months. Therefore, the dose selected for this study is consistent with current use of the medication and the dose intervals are shorter than current practice.

4.3. Selection of Study Population

4.3.1. Asymptomatic Population

The inclusion and exclusion criteria for the asymptomatic population are excerpted below from the Study Protocol, Version 4.0, the earliest protocol version under which subjects were enrolled.

4.3.1.1. Inclusion Criteria, Asymptomatic Population

1. Provide written informed consent prior to initiation of any study procedures.
2. Able to understand and comply with planned study procedures and be available for all study visits.
3. Male or non-pregnant female 18-65 years of age, inclusive.
4. Amebiasis or giardiasis identified by positive TechLab antigen test, positive wet mount or trichome (confirmed by PCR), and positive stool PCR for E. histolytica or Giardia.[1]

   [1]If a subject is infected with both E. histolytica and Giardia, they will be enrolled in the E. histolytica study arm. Once the Entamoeba study arm is fully enrolled, any subsequent dual infected subjects will be enrolled in the Giardia arm.

5. In otherwise good health[2].

   [2]As determined by medical history and targeted physical examination, if indicated based on medical history, to evaluate acute or currently ongoing chronic medical diagnoses or conditions that would affect the assessment of eligibility and safety of subjects. Existing medical diagnoses or conditions (except those in the Subject Exclusion Criteria) must be deemed as stable chronic medical conditions. A stable chronic medical condition is defined as no change in prescription medication, dose, or frequency of medication in the last 3 months (90 days) and health outcomes of the specific disease are considered to be within acceptable limits in the last 6 months (180 days). Any change due to change of health care provider, insurance company, or that is done for financial reasons, as long as in the same class of medication, will not be considered a violation of this inclusion criterion. Any change in prescription medication due to improvement of a disease outcome, as determined by the site principal investigator or

appropriate sub-investigator, will not be considered a violation of this inclusion criterion. Subjects may be on chronic or as needed (prn) medications if, in the opinion of the site principal investigator or appropriate sub-investigator, they pose no additional risk to subject safety. Topical, nasal, and inhaled medications, vitamins, and contraceptives are permitted.

6. Vital signs (oral temperature, pulse, and blood pressure) are all within normal protocol-defined ranges (abnormal criteria defined in Section 9.2.3).
7. Laboratory tests (blood urea nitrogen, creatinine, AST, ALT, white blood cells, platelets, hemoglobin) are all within protocol-defined reference ranges[3].

[3]The normal ranges for Icddr,b laboratory tests include (a) blood urea nitrogen (BUN) between 5 and 24 mg/dL, inclusive, (b) creatinine between 53 and106 umol/L, inclusive, males and between 44 and 97umol/L, inclusive, for females, (c) AST of 38 U/L or less for males and 32 U/L or less for females (d) ALT of 41.0 U/L or less for males and 31 U/L or less for females, (e) WBC between 4.0 and 11.0 10^9/L, inclusive (f) platelets between 150 and 450 10^9/L, inclusive, (g) hemoglobin between 12.5 and 17.5 gm/dL, inclusive, for males and 11.5 and 16.5 gm/dL, inclusive, for females,

Subjects will be eligible for enrollment with the following laboratory values:

- Blood urea nitrogen less than 30 mg/dL
- Creatinine less than 133 umol/L
- AST or ALT less than 60.0 U/L
- White cell count between 3.5 and 11.0 (109/L)
- Platelets between 100 and 500 (109/L)
- Hemoglobin between 11.0 and 18.0 gm/dL

8. Urinalysis with no greater than trace protein. If a high protein is confirmed to be due to menstruation, it should be repeated.
9. Women of reproductive potential[4] must have a negative urine pregnancy test within 72 hours of starting study medications.

[4]Female subjects who are surgically sterile via tubal sterilization, bilateral oophorectomy or hysterectomy or who have been postmenopausal for greater than 1 year are not considered to be of reproductive potential.

10. Female subjects participating in sexual activity that could lead to pregnancy must agree to use highly effective[5] contraception while receiving auranofin and for 15 weeks after.

[5]Highly effective methods of contraception are defined as having low failure rates (i.e. less than 1% per year) when used consistently and correctly and may include, but are not limited to, abstinence from intercourse, monogamous relationship with a vasectomized partner, male condoms with spermicide, diaphragm with spermicide, intrauterine devices, and licensed hormonal methods. If an eligible female of child-bearing potential is not using effective contraception, hormonal contraceptives will be supplied to female subjects and condoms will be provided for her partner while they are on the trial and for the follow-up period of 4 months total. Females on effective forms of birth control will continue while on the study and for the follow-up period of 4 months total and also be provided condoms for their partners. The method and compliance of birth control used will be confirmed and documented at all study visits.

4.3.1.2. Exclusion Criteria, Asymptomatic Population

Subjects meeting any of the following exclusion criteria at baseline will be excluded from study participation within 1 week of the initial visit:

1. Known intolerance of auranofin or gold compounds.
2. Pregnant or breastfeeding women or women who plan to become pregnant or breastfeed at any given time during the study or within 2 months of study completion.
3. Diarrhea (> 3 loose stools/ 24 hours) within 7 days prior to starting study medications.
4. Anticipated travel of more than 50 km from study site planned in next month.
5. Current use of systemic antibiotics or metronidazole.
6. Has any condition that would, in the opinion of the site investigator, place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol.
7. Concurrent participation in other investigational protocols or receipt of an investigational product within the previous 30 days.
8. History of alcohol or drug abuse within the last five years.

4.3.2. Symptomatic Population

The inclusion and exclusion criteria for the symptomatic population are excerpted below from the Study Protocol, Version 7.0.

4.3.2.1. Inclusion Criteria, Symptomatic Population

1. Provide written informed consent prior to initiation of any study procedures.
2. Able to understand and comply with planned study procedures and be available for all study visits.
3. Male or non-pregnant, non-lactating females 18-65 years of age, inclusive. Females of reproductive potential currently using effective contraceptive methods are eligible.
4. Amebiasis or giardiasis identified by rapid EIA and positive antigen detection EIA of stool[1]

   [1]If a subject is infected with both *E. histolytica* and *Giardia,* they will be enrolled in the *E. histolytica* study arm. Once the *Entamoeba* study arm is fully enrolled, any subsequent dual infected subjects will be enrolled in the *Giardia* arm. If a subject is infected with both *Giardia* and *Cryptosporidium,* they will not be enrolled.

5. Has diarrhea (defined as three or more loose stools) in the past 24 hrs, but is assessed to be clinically stable and in otherwise good health[2].

   [2]As determined by medical history and targeted physical examination, if indicated based on medical history, to evaluate acute or currently ongoing chronic medical diagnoses or conditions that would affect the assessment of eligibility and safety of subjects. Existing medical diagnoses or conditions (except those in the Subject Exclusion Criteria) must be deemed as stable chronic medical conditions. A stable chronic medical condition is defined as no change in prescription medication, dose, or frequency of medication in the last 3 months (90 days) and health outcomes of the specific disease are considered to be within acceptable limits in the last 6 months (180 days). Any change due to change of health care provider, insurance company, or that is done for financial reasons, as long as in the same class of medication, will not be considered a violation of this inclusion criterion. Any change in prescription medication due to improvement of a disease outcome, as determined by the site principal investigator or appropriate sub-investigator, will not be considered a violation of this inclusion criterion. Subjects may be on chronic or as needed (prn) medications if, in the opinion of the site principal investigator or appropriate sub-investigator, they pose no additional risk to subject safety. Topical, nasal, and inhaled medications, vitamins, and contraceptives are permitted.

6. Vital signs (oral temperature, pulse, and blood pressure) are all within normal protocol-defined ranges
7. Laboratory tests (blood urea nitrogen, creatinine, AST, ALT, white blood cells, platelets, hemoglobin) are all within protocol-defined ranges.

   Subjects will be eligible for enrollment with the following laboratory values:

   - Blood urea nitrogen less than or equal to 30 mg/dL
   - Creatinine less than or equal to 133umol/L
   - AST or ALT less than or equal to 70.0 U/L
   - White cell count between 3.5 and 13.0 inclusive(10^9/L)
   - Platelets between 131 and 550 (10^9/L) inclusive
   - Hemoglobin between 11.0 and 18.0 gm/dL inclusive
8. Urinalysis with no greater than trace protein. If a high protein is confirmed to be due to menstruation, it should be repeated.
9. Women of reproductive potential[4] must have a negative urine pregnancy test within 72 hours of starting study medications.

   [4]Female subjects who are surgically sterile via tubal sterilization, bilateral oophorectomy or hysterectomy, who have been postmenopausal for greater than 1 year are not considered to be of reproductive potential.

10. Female subjects participating in sexual activity that could lead to pregnancy must be using and continue to use highly effective[5] contraception for a total of 4 months after enrollment.

    [5]Highly effective methods of contraception are defined as having low failure rates (i.e. less than 1% per year) when used consistently and correctly and may include, but are not limited to, abstinence from intercourse, monogamous relationship with a vasectomized partner, male condoms with spermicide, diaphragm with spermicide, intrauterine devices, and licensed hormonal methods. Females on effective forms of birth control will continue while on the study and for the follow-up period of 4 months total. The method and compliance of birth control used will be confirmed and documented at all study visits.

4.3.2.2. Exclusion Criteria, Symptomatic Population

Subjects meeting any of the following exclusion criteria at baseline will be excluded from study participation within 1 week of the initial visit:

1. Known intolerance of auranofin or gold compounds.
2. Pregnant or breastfeeding women or women of reproductive potential not using effective contraception or who plan to become pregnant or breastfeed at any given time during the study or within 3 months of study completion.
3. Use of metronidazole within the past 7 days.
4. Has any condition that would, in the opinion of the site investigator, place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol.
5. Concurrent participation in other investigational protocols or receipt of an investigational product within the previous 30 days.
6. History of alcohol or drug abuse within the last five years.

4.3.3. Reasons for Withdrawal

Subjects may voluntarily withdraw their consent for study participation at any time and for any reason, without penalty. Subjects who have received study product, regardless of the number of doses received, or who developed an AE or SAE will be encouraged to remain in the study to be followed for safety purposes.

A subject may withdraw or be withdrawn from this study for any of the following reasons:

1. Medical disease or condition, or any new clinical findings for which continued participation, in the opinion of the site principal investigator or appropriate sub-investigator, would compromise the safety of the subject, or would interfere with the subject's successful completion of the study, or would interfere with the evaluation of responses.
2. Subject no longer meets eligibility criteria.
3. As deemed necessary by the site principal investigator or appropriate sub-investigator for noncompliance or other reasons.
4. Subject withdrawal of consent.
5. Subject lost to follow-up.
6. Termination of the study.
7. New information becomes available that makes further participation unsafe.
8. A subject will be discontinued from further receipt of auranofin or placebo if:
    a. The subject misses more than one dose of drug or placebo.
    b. Any clinical adverse event, laboratory abnormality, intercurrent illness, other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.

4.4. Treatments

4.4.1. Treatments Administered

Auranofin (2, 3, 4, 6-tetra-O-acetyl-1-thio-D-glucopyranosato-S) (triethyl-phosphine gold), is an orally available gold-containing compound with established pharmacology and is approved for human use by the FDA. It is available in an oral form as capsules called Ridaura, which contain 3 mg of auranofin per capsule. Auranofin 3 mg capsules are manufactured by Prometheus Laboratories, San Diego, CA. Subjects assigned to receive auranofin receive daily doses of 6 mg (two capsules) for either 7 days (amebiasis group) or 5 days (giardiasis group).

Each capsule of auranofin has an opaque brown cap and opaque tan body, contains 3 mg of white crystalline powder, and is imprinted with the product name RIDAURA. Inactive ingredients consist of benzyl alcohol, cellulose, cetylpyridinium chloride, D&C Red No. 33, FD&C Blue No. 1, FD&C Red No. 40, FD&C Yellow No. 6, gelatin, lactose, magnesium stearate, povidone, sodium lauryl sulfate, sodium starch glycolate, starch, titanium dioxide and trace amounts of other inactive ingredients. Auranofin 3 mg capsules are packaged in bottles of 60 count.

The placebo capsules are similar to auranofin capsules with opaque brown caps and an opaque tan body, but are not imprinted with the product name RIDAURA. They are manufactured by a contract supplier through

Fisher BioServices. In order to mitigate potential unblinding of subjects and staff dispensing medication, the pharmacist will dispense daily doses according to the randomization assignment into dark, amber, light-protective bottles with secure cap. Each bottle will contain a daily dose (two capsules), so subjects in the giardiasis group will have 5 bottles; those in the amebiasis group will have 7 bottles. Each individual bottle containing the single dose will be labeled with barcode and with randomization code and subject ID (as per local SOP) and double-checked before dispensing (i.e., before leaving the pharmacy and going out to the Mirpur Clinic). The containers used to store the capsules are tight and light-resistant and will be identical for the placebo and auranofin capsules.

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

Per International Conference on Harmonisation (ICH) guideline E6: Good Clinical Practice (GCP), screening records will be kept at the icddr, b site to document the reason why an individual was screened, but failed trial entry criteria. The reasons why individuals failed screening will be recorded in the Statistical and Data Coordinating Center's (SDCC) Advantage eClinical Electronic Data Capture System.

In the asymptomatic population, eligible subjects were stratified by disease strata (amebiasis or giardiasis), and then within each stratum, randomized 1:1 to receive auranofin or placebo. Enrollment was to continue in the other stratum after one stratum reached full enrollment. All subjects were to receive doses of the assigned medication or placebo delivered orally on Days 1, 2, 3, 4, 5, 6, and 7 for amebiasis and Days 1, 2, 3, 4, and 5 for giardiasis.

For the symptomatic population, randomization is stratified by site to prevent confounding that could arise from imbalance in treatment allocations between sites. Because the relative pace of enrollment between the two sites is unknown, the number of participants to be enrolled at each site is not fixed in advance. With this approach, the faster enrolling site may enroll more subjects, allowing enrollment to complete as quickly as possible. Each site may enroll up to 68 subjects into each stratum, so it is possible that one stratum could be filled entirely with subjects from a single site. With this flexible approach, treatment assignments may not be perfectly balanced (overall or within each site), but they will be approximately balanced. With sample sizes of 68 in each stratum, the impact of a small imbalance on power is negligible. Once eligibility and consent are confirmed, symptomatic subjects are stratified by site and infection (amebiasis or giardiasis), and then within each stratum, randomized 1:1 to receive auranofin or placebo. Enrollment will continue in the other arm after one arm reaches full enrollment. All subjects receive the assigned medication or placebo delivered orally on Days 1, 2, 3, 4, 5, 6, and 7 for amebiasis and Days 1, 2, 3, 4, and 5 for giardiasis.

The randomization codes were prepared by statisticians at the SDCC and included in the enrollment module for the trial. SDCC staff generated the randomization lists for each study population and site and sent corresponding documentation to the study sites. The randomization lists include the randomization codes to serially assign study treatment to subjects as they are assigned to the study (i.e., randomize subjects to study arm by study identification number). This table did not contain unblinded information; study staff were not able to see the study arm assignment for each study identification number.

Eligible study subjects were to be randomized under single-blind conditions by study staff members after consent. Since the placebo is similar but not identical to the study medication, only the lab personnel are truly blind, however the participants were not to be informed whether they receive study product or placebo. The randomization numbers were to be recorded on the study CRFs.

A designated individual at each site (icddr,b and Rajshahi Medical College hospital) was provided with the treatment key, which links the treatment code to the actual treatment assignment. This is kept in a secure place.

4.4.3. Blinding

The unblinded pharmacist at the site will refer to the electronic treatment key provided for the trial by the SDCC to determine the treatment assignments for the subjects. The pharmacist will maintain a hard copy of the treatment key (provided by the SDCC) under locked/secured conditions and will follow the randomization code.

As described in Section 4.4.1 above, the placebo and auranofin capsules are similar in appearance, but not perfectly identical. They will be stored in identical containers. Study staff administering them and study subjects will not be informed of their minor differences in appearance nor of the treatment assignments of subjects. The treatment assignment codes used by staff administering the medication will not reveal the treatment assignments of subjects. In addition, the laboratory personnel performing evaluations will be blinded to treatment assignment.

The protocol contains no explicit provisions for emergency unblinding. According to DMID policy, the study medical monitor responds to requests for emergency unblinding, and instructs the SDCC to release treatment codes only if necessary, to ensure that the subject receives appropriate clinical care.

4.5. Efficacy and Safety Variables

4.5.1. Efficacy Variables

Table 4 and Table 5 summarize the efficacy variables and time points for the asymptomatic and symptomatic populations, respectively.

Table 4: Efficacy Variables for the Asymptomatic Study Population

Outcome Type	Outcome	Time points, Asymptomatic amebiasis group	Time points, Asymptomatic giardiasis group
Primary	Parasitological response (no detection of cysts or trophozoites on microscopic exam or negative antigen detection)	Day 7	Day 5
Secondary	Parasitological response (no detection of cysts or trophozoites on microscopic exam or negative antigen detection)	Days 3 and 5	Day 3
	Rate of decrease in trophozoite/cyst load by qPCR in stools	Days 3, 5, and 7	Days 3 and 5
	Negative stool antigen test	Days 3, 5, 7, and 14	N/A
	Sustained cure (no detection of cysts or trophozoites by microscopic exam or negative antigen detection)	Days 14 and 28	Days 14 and 28
	Relapse (same strain) or re-infection (new strain) with positive stools by genotyping the initial vs. subsequent strain.	Day 14 and/or 28	Day 14 and/or 28

Table 5: Efficacy Variables and Time Points for the Symptomatic Study Population

Changes from outcomes for the asymptomatic population are shown in blue:

Outcome Type	Outcome	Time points, Symptomatic amebiasis group	Time points, Symptomatic giardiasis group
Primary	Resolution of diarrhea [a]	Day 7	Day 5
Secondary	Parasitological response (no detection of trophozoites on microscopic exam [b])	Days 3, 5, and 7 [c]	Day 3 and 5 [c]
	Rate of decrease in trophozoite/cyst load by qPCR in stools	Days 3, 5, and 7	Days 3 and 5
	Negative stool antigen test	Days 3, 5, 7, and 14	Days 3 and 5
	Sustained cure (no detection of trophozoites by microscopic exam) [d]	Days 14 and 28	Days 14 and 28
	Relapse (same strain) or re-infection (new strain) with positive stools by genotyping the initial vs. subsequent strain.	Day 14 and/or 28	Day 14 and/or 28
	Time to resolution of diarrhea	Assessment over the study period	Assessment over the study period

[a] New outcome for the symptomatic population
[b] The definition of parasitological response was revised to allow for cysts and remove the antigen test.
[c] Moved from primary to secondary outcome.
[d] The definition of "cure" was updated to match the updated definition of "parasitological response".

Diarrhea will be assessed by self-report at each study visit. All other primary and secondary outcomes for both disease groups are measured on stool samples. Subjects will provide stool samples on Days 1, 3, 5, 7(window +1 day), 14 (window +3 days) and 28 (window +3 days). The specimen will be stored in a cooler with ice pack for transport to the laboratory. All laboratory personnel will be blinded, and the specimens de-identified.

a. Testing of stool samples will be performed by the icddr,b Parasitology Laboratory or Rajshahi Hospital laboratory and will include:
   i. Wet mount for ova and parasite examination;
   ii. TechLab EIA to detect *E. histolytica* and *Giardia* to identify protozoal infections;
   iii. PVA fixation for concentration and trichrome staining for ova and parasite examination
   iv. Qualitative PCR to detect *E. histolytica* and *Giardia*

b. Off-site testing of stool samples at UCSD will include quantitative E. histolytica or Giardia testing performed at UCSD on shipped aliquots of DNA extracted from positive stools at icddr, b. De-identified DNA specimens labeled with the subject code will be obtained from stools on Days 1, 3, 5, 7, 14, and 28 following enrollment. Quantitative PCR assays have been developed based on the small subunit rRNA gene, which is highly conserved among E. histolytica (Taniuchi, 2011) and Giardia isolates (Haque, 2007).

Safety variables include solicited adverse events, vital signs, and clinical labs. These are the same for the two disease groups and study populations. The only exception is that although diarrhea is recorded for both populations, it is considered an efficacy rather than safety variable for the symptomatic population, because it is an eligibility criterion and an efficacy endpoint. In other words, since everyone enrolls with diarrhea, their

subsequent diarrhea is probably not due to the treatment. Solicited events and vital signs are recorded during planned visits until the Day 28 visit. Vital signs are recorded during every planned follow-up visit.

Solicited events are AEs that are known to occur with this study product. Adverse event data is collected at each visit using specific questions and/or targeted physical examination. Based on the adverse reactions listed on the package insert, these include: loose stools or diarrhea, abdominal pain, nausea with or without vomiting, constipation, anorexia, flatulence, dyspepsia, dysgeusia, pruritus, hair loss, urticarial, stomatitis, conjunctivitis, glossitis, hematuria, and rashes. As noted above, diarrhea is considered an adverse event only in the asymptomatic population as it is a condition for enrollment in the symptomatic population. Physical examinations look for abdominal pain, hair loss, urticaria, rashes, stomatitis, conjunctivitis, and glossitis. In the symptomatic population, solicited AEs are not collected that are related to any prescribed metronidazole. Adverse event collection continues until Day 28 (following three half-lives of the drug). Each solicited adverse event described above is graded as Mild (Grade 1) if it "Does not interfere with daily activity", as Moderate (Grade 2) if it "Interferes with daily activity", and as Severe (Grade 3) if it "Prevents daily activity (incapacitating)". Grading for vital signs, also collected on every visit, is given in Table 6. Furthermore, hematology, biochemistry, and urine labs are analyzed on Study Day 7. Grading for these adverse events is given in Table 7. Some laboratory grading ranges were modified in protocol updates; these modifications are displayed in the table. Laboratory results are graded according to the protocol effective on the date the sample was collected. The effective date is the date that the site received IRB approval for the version and began implementing that version. (The effective date is later than the protocol version date, which indicates when the version was approved by DMID.) The first subjects in the study enrolled under Protocol Version 4.0, so laboratory ranges for earlier protocol versions are not displayed. The effective dates are as follows: Version 4.0: 18Oct2016, Version 5.0: 12Dec2017, Version 6.0: 07Aug2018, Version 7.0: 23Jul2019.

Table 6: Vital Signs Grading Scale

Vital Signs*			
Vital Signs	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Fever (°C) **	37.8-38.4	38.5-38.9	>= 39.0
Hypertension (systolic) mm Hg	141-150	151-155	>155 or an ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) mm Hg	91-95	96-100	>100 or an ER visit or hospitalization for malignant hypertension
Hypotension (systolic) mm Hg	85-89	80-84	<80 or an ER visit or hospitalization for hypotensive shock
Bradycardia – beats per minute ***	50-54 or >10 bpm less than baseline if baseline < 60	45-49 or >15 bpm less than baseline if baseline < 60	<45 or > 20 BPM or less than baseline if baseline < 60, or an ER visit or hospitalization for arrhythmia
Tachycardia – beats per minute	101-115	116-130	>130 or an ER visit or hospitalization for arrhythmia

* Subjects should be at rest for at least 15 minutes prior to vital sign measurements
** Oral temperature; no recent hot or cold beverages or smoking
*** When resting heart rate is between 60-100 beats per minute. Pulse and Blood Pressure assessed at Visit 1 (Day 1) will be considered baseline. Sinus bradycardia among some healthy subject populations, for example, conditioned athletes maybe acceptable

Table 7: Laboratory Adverse Event Grading Scale

NOTE: For grading ranges that were updated in protocol revisions, all ranges are shown in the below table, with their corresponding protocol versions. No subjects were enrolled under Protocol Versions 1-3, so ranges from those versions are omitted. Events are graded according to the protocol version that was active at the time of the event. Effective dates are: Version 4.0: 18Oct2016, Version 5.0: 12Dec2017, Version 6.0: 07Aug2018, Version 7.0: 23Jul2019

Hematology	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
WBC 10^9/L (Decrease)	Version 4: 3.0-3.9 Versions 5-7: 3.0 – 3.4	2.0-2.9	<2.0
WBC 10^9/L (Increase)	Version 4: 11.1-13.0 Versions 5-7: 13.1-13.9	Version 4: 13.1-15.0 Versions 5-7: 14.0-15.0	>15.0
Hgb g/dL (Decrease) (Female)	Versions 4-6: 9-11.4 Version 7: 9.1-10.9	7.5-9.0	<7.5
Hgb g/dL (Decrease) (Male)	Versions 4-6: 9-12.4 Version 7: 9.1-10.9	7.5-9.0	<7.5
Hgb g/dL (Increase)	Versions 4-6: N/A Version 7: 18.1-18.5	Versions 4-6: N/A Version 7: 18.6-19.0	Versions 4-6: N/A Version 7: >19.0
Platelets 10^9/L (Decrease)	Version 4: 100-149 Versions 5-7: 100-130	50-99	<50
Platelets 10^9/L (Increase)	Version 4: 451-480 Versions 5-7: 551-600	Version 4: 480-500 Versions 5-7: 601-700	Version 4: >500 Versions 5-7: >700

Chemistry	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
BUN mg/dL	Version 4: 25-60 Versions 5-7: 31-60	Versions 4-7: 60-70† Version 8: >60 and ≤70	>70
Creatinine umol/L[1] (Increase) (Male)	Version 4: 107-176 Versions 5-7: 134-176	177-221	>221
Creatinine umol/L[1] (Increase) (Female)	Version 4: 98-161 Versions 5-7: 134-176	Version 4: 162-202 Versions 5-7: 177-221	Version 4: >202 Version 5-7: >221
AST IU/L males (Increase)	Version 4: 38.1-200 Version 5: 60.1-200 Versions 6 and 7: 70.1-200	201-300	>300
AST IU/L females (Increase)	Version 4: 32.1-200 Version 5: 60.1-200 Versions 6 and 7: 70.1-200	201-300	>300
ALT IU/L males (Increase)	Version 4: 41.1-200 Version 5: 60.1-200 Versions 6 and 7: 70.1-200	201-300	>300
ALT IU/L females (Increase)	Version 4: 31.1-200 Version 5: 60.1-200 Versions 6 and 7: 70.1-200	201-300	>300

Urinalysis	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Protein	1+	2+	3+ or hospitalization or dialysis

[1]Conversion factor from mg/dL: http://onlinelibrary.wiley.com/doi/10.1002/97808138188825.app3/pdf
[2]Trace protein at screening (Visit 00B) is acceptable for inclusion into the study.
† Values of 60 fall into both Mild and Moderate categories for protocol versions 4-7 and will be classified as Mild.

5. SAMPLE SIZE CONSIDERATIONS

The primary amebiasis outcome for this study is to compare the proportion of patients/subjects with resolution of diarrhea by Day 7 of therapy, in which placebo is expected to have a clearance rate of approximately 15-20%. Sample size calculations for both primary endpoints are based on a two-sample, two-sided binomial test for proportions, with alpha set to 0.05. Calculations were performed using the R statistical package (Version 3.0.2; http://www.r-project.org). The primary amebiasis endpoint in this aim is to compare the resolution of diarrhea between the two study arms to demonstrate that auranofin increases resolution of diarrhea. For this power analysis, we assume the following: a predicted diarrhea resolution rate of at least 80% (based on treatment results with current standard therapy with metronidazole [1]) in the auranofin treatment group.

With these assumptions, assuming 10% attrition (determined from the average of multiple other clinical trials in the same Mirpur district), a sample size of 68 with amebiasis (34 per arm; 60 completers in total) achieves greater than 95% power to detect a difference between the group proportions of 60%. The high statistical power for the primary endpoint is planned to also ensure adequate power for the secondary endpoints.

For the primary giardiasis endpoint of proportion of subjects with clearance of Giardia by Day 5, a similar sample size of 34 per arm will achieve 85% power to detect a 40% difference between treatment arms with a predicted clearance rate of 70% (based on response rates to metronidazole or tinidazole, Gardiner, 2001) and a 30% clearance rates in placebo.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

Continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for categorical measures. In general, all data will be listed, sorted by disease group, site, treatment and subject, and when appropriate by visit number within subject. In general, summary tables will be created separately for the four populations (asymptomatic amebiasis, asymptomatic giardiasis, symptomatic amebiasis, and symptomatic giardiasis), and will include columns for each treatment in the order (Auranofin, Placebo) and will be annotated with the total population size relevant to that table/treatment.

6.2. Timing of Analyses

There will be no planned interim analyses for efficacy or futility conducted for this study, but the DSMB may modify this during ongoing safety monitoring.

Asymptomatic subjects (34) enrolled under Versions 1-4 of the protocol will have their data reviewed and clinical database locked for analysis first and a separate report generated. This may be generated before follow-up is completed in the symptomatic study population.

In the event that recruitment and follow-up for either the Giardiasis arm or the Amebiasis arm is completed ahead of the other, the primary and secondary endpoints may be analyzed for that arm using the specified methods. This report will be considered the interim CSR and will contain detailed unblinded information about the participants, their immunological response to treatment as well as their side effects and any laboratory abnormalities. The interim CSR will be followed with a release of data corresponding to the report.

6.3. Analysis Populations

The primary analysis population is the modified Intention-to-Treat (mITT) population, described in 6.3.1 below. All primary and secondary endpoints will be conducted on both the modified Intention-to-Treat population and the per-protocol population, described in Sections 6.3.1 and 6.3.2, respectively. Tabular listings of all subjects excluded from each of these populations are provided, separately for each disease group, in Listing 7 and Listing 8.

6.3.1 Modified Intention-to-Treat (mITT) Population

In this study, the primary analysis will be performed on the mITT population. This population was defined in the protocol to include study participants who were randomized and dispensed at least one dose of study medication. However, as described in section 6.3.1.1 below, those who failed the eligibility criterion regarding testing positive for amebiasis or giardiasis will be excluded. Excluding subjects who were not dispensed study medication has the potential to introduce bias in estimates if the dispensation of medication is influenced by treatment assignment. Although this study is not perfectly blinded, the procedures for distributing medication are designed to reduce the possibility of un-blinding the staff dispensing medication (see Section 4.4.3). These procedures ensure that study staff dispensing medication will not be able to identify the treatment assignment of subjects prior to dispensing the first dose of treatment. Therefore, it is

unlikely that bias will be introduced by excluding subjects who did not receive at least one dose. The possibility of bias will be assessed by comparing dispensation rates between the treatment and control groups.

6.3.1.1. Exclusions Due to Violation of Eligibility Criteria

Furthermore, subjects who meet the primary outcome at baseline (and therefore should not have been enrolled) will be excluded from the mITT population. In the asymptomatic population, the outcome is a negative microscopy or antigen test at Day 5 or 7, so subjects were required to have both positive microscopy result and positive test result for their respective disease in order to enroll. Those who did not will be excluded.

In the symptomatic population, subjects were to have amebiasis or giardiasis identified by rapid EIA and positive antigen detection at enrollment in order to be eligible. The primary outcome is resolution of diarrhea by Day 5 or 7. Those who either failed the eligibility criterion (i.e., had a negative EIA or negative antigen test), or did not have diarrhea at enrollment, will be excluded from the mITT population.

6.3.2. Per Protocol Population

As a secondary analysis, a per-protocol (PP) population will be analyzed. The per-protocol population will consist of all data from subjects who did not substantially deviate from the protocol during the time leading up to (and including) the collection of the data point in question. Missed or out-of-window stool samples from prior visits will not be considered protocol deviations as long as the stool sample for the visit of interest (for a particular outcome) is provided within window. For example, if a stool sample was not provided on Day 3, but is provided on Day 5, this stool sample will be included for analysis of endpoints on Day 5. Subjects who completed at least 80% of the treatment regimen will be included in the per-protocol population. This corresponds to at most a single missed dose during the course of treatment, since the amebiasis group has seven required doses (and 6/7=86%) and the giardiasis group has five required doses (and 4/5=80%). If a large number of subjects missed a single dose, we will perform sensitivity analysis by also analyzing the population of subjects with 100% compliance. Endpoints that are measured out of window will be excluded from this analysis.

All exclusions described in Section 6.3.1.1 (Exclusions due to violation of eligibility criteria) also apply to the PP Population.

Subjects may also be removed from this population as determined on a per-subject basis by the PI and the DMID Scientific Lead prior to unblinding.

6.3.3. Safety Population

The safety population will consist of all subjects who received any study product (including control). This population will be summarized according to the actual treatment received.

6.4. Covariates and Subgroups

All analyses will be performed separately for the two disease groups (amebiasis and giardiasis). Apart from disease strata, the protocol does not formally define any subgroup analyses, and the study is not adequately powered to perform subgroup analyses.

6.5. Missing Data

The primary analysis involves comparison of a binary response between the treatment group and the placebo group. This is true for both asymptomatic and symptomatic populations, whose primary outcomes are parasitological response and resolution of diarrhea, respectively. Within each population, the response is measured at Day 7 for the amebiasis group and Day 5 for the giardiasis group. In the symptomatic population, subjects who terminate their treatment regimen and receive metronidazole due to worsening symptoms will be imputed as treatment failures for the primary outcome. That is, they will be imputed as still symptomatic by Day 7 in the amebiasis group, and by Day 5 in the giardiasis group. Secondary outcomes measured at Days 3, 5, and 7 will be imputed analogously, with the exception of the quantitative trophozoite/cyst load.

The rest of the text in this section applies to both asymptomatic and symptomatic populations.

In the primary analysis, no covariates are included, so the analysis involves two variables: the binary predictor (treatment/placebo) and the binary response (parasitological response: yes/no). Some subjects may have missing values for the response variable, for example, if they are unable to provide a stool specimen on the designated day. If all subjects are equally likely to have missing response values, then the data are Missing Completely At Random (MCAR), in which case these subjects may be dropped from analysis without biasing the results. If, on the other hand, missingness depends on other values which are observed, then the data are Missing At Random (MAR). It is possible that the data in this study will be MAR but not MCAR (which is a more stringent condition). For example, it is plausible that subjects in the auranofin group will be more likely to miss a stool specimen than those in the placebo group since constipation is one known possible side effect of auranofin. If this is the case, and if those who are missing response values in the auranofin group also experience a different response to treatment than those who remain in the study, then dropping these subjects from analysis will bias the estimate of the treatment effect. An appropriate approach to remove the bias from dropping these subjects from analysis is multiple imputation, which is proposed below. A third possibility for the missingness mechanism is that the missingness depends on one or more unobserved variables (and may depend on observed variables, as well). As all relevant symptom variables, as well as demographic variables, will be measured, it is unlikely that missingness pattern will depend on an unobserved variable. For the symptomatic population, microscopy results will also be evaluated as a predictor.

Multiple imputation will be used to handle missing response values for the primary analysis. Multiple imputation is a method in which observed covariates are used to predict missing values, and the uncertainty arising from this imputation procedure is incorporated into final treatment effect estimates. Single imputation methods, such as imputing treatment failures for all missing results, result in unrealistically small standard errors as the imputed counts are less variable than real data. In contrast, multiple imputation methods can provide valid standard error estimates. Multiple imputation methods fill in missing values repeatedly, creating multiple sets of completed datasets. For each of the datasets, point estimates and standard errors are computed. These estimates and standard errors are then combined to obtain the multiple imputation estimate and standard error estimate [2].

As our response variable is binary, logistic regression will be used for the multiple imputation procedure. In order to determine which covariates to include as predictors of missingness, tests of association between all baseline variables and missingness will be performed (t-tests, chi-square tests, or Fisher's exact tests, as appropriate). If appropriate, t-tests will be performed on transformed data, although sample size is likely large enough that transformation will not be required. Covariates whose p-values are greater than 0.10 will be included in the imputation model. Symptom variables including constipation, diarrhea, anorexia, nausea,

abdominal pain, whether or not the subject had any other AE, and whether or not the subject withdrew from the study due to an AE will be evaluated for inclusion through the same criterion. For the symptomatic population, microscopy results will be evaluated as well.

Next, the imputation procedure proceeds as follows:

1. *Imputation step*. In this step, multiple copies of the original data set are generated, and missing values of the response variable in each copy are imputed based on a logistic regression model which includes baseline variables as predictors as well as study variables measured after baseline. The imputed data sets will vary in their imputed values but will have identical non-missing values. The generation of multiple imputed data sets enables us to quantify the uncertainty arising from the imputation process.
2. *Analysis step.* On each imputed data set, the primary analysis will be performed: computing the difference in proportions of parasitological response between treatment and placebo arms, as well as the standard error for the difference in proportions. The odds ratio and respective standard error will be computed as well.
3. *Combination step.* The imputed data sets are combined to obtain a single estimate for the difference in proportions and standard error, and a single estimate for the odds ratio and standard error.

The secondary analysis includes a per-protocol analysis including only participants with completely observed data. This analysis requires the data to be MCAR, a more stringent condition than MAR.

All except one of the secondary outcomes are also binary, so will be analyzed through the same imputation method. The sole numeric outcome is parasite load, measured at multiple time points and analyzed with a mixed effects model for longitudinal data. The mixed effects model, described below, adjusts for data that are missing at random (MAR), so imputation is not required in that analysis.

6.5.1. Sensitivity Analyses

The primary analysis assumes that missing data are missing at random – i.e. the missingness depends only on the values of observed variables. This is an assumption which cannot be proven. Although we can show that missingness is related to values of observed variables (suggesting MAR and proving that MCAR does not hold), it is impossible to prove that there is no non-observed variable related to missingness.

However, we can assess whether MCAR is satisfied – the condition required for our per-protocol analysis. To do so, we will test for associations between all covariates and missingness with t-tests, chi-square tests, and/or Fisher's exact tests, as appropriate. The results of the logistic regression model predicting missingness based on the combination of covariates will also be reported and discussed.

6.6. Interim Analyses and Data Monitoring

There will be no planned interim analyses for efficacy or futility conducted for this study, but the DSMB may modify this during ongoing safety monitoring. The study team will review all adverse events by cumulative reports on a monthly basis. Adverse events will be graded using the protocol defined grading system. The DSMB, established by the study team, will monitor this study.

The DSMB will review the safety data when the study reaches 50% enrollment (i.e. 34 subjects enrolled per parasite group). The DSMB will review safety data after the 68th subject completes visit 8.

Asymptomatic subjects (34) enrolled under Version 1-4 of the protocol will have their data reviewed and clinical database locked for analysis first and a separate report generated. This may be generated before follow-up is completed in the symptomatic study population.

In the event that recruitment and follow-up for either the Giardiasis arm or the Amebiasis arm is completed ahead of the other, the primary and secondary endpoints may be analyzed for that arm using the specified methods. This report will be considered the interim CSR and will contain detailed unblinded information about the participants, their immunological response to treatment as well as their side effects and any laboratory abnormalities. The interim CSR will be followed with a release of data corresponding to the report.

6.7. Multiple Comparisons/Multiplicity

For each study population (asymptomatic, symptomatic) and disease group (amebiasis, giardiasis) there is a single primary endpoint. This can be viewed as four parallel studies. No adjustments for multiple testing are planned.

7. STUDY SUBJECTS

7.1. Disposition of Subjects

Table 14 will present a summary of the reasons that subjects were screened but not enrolled. The table will be repeated for each study population.

The disposition of subjects in the study will be tabulated by treatment group, separately for each disease group and study population (Table 9 and Table 10). The table shows the total number of subjects screened, the number that enrolled and received at least 1 dose, the number that received all scheduled doses, and the number that completed stool sample for the primary endpoint (day 5 for the giardiasis group; day 7 for the amebiasis group).

A flowchart showing the disposition of study subjects, adapted from the Consort Statement (Drummond, 2001) is included (Figure 3). This figure will present the number of subjects screened, enrolled, lost to follow-up, and analyzed, by treatment arm. A separate flowchart will be created for each study population.

The composition of analysis populations, including reasons for subject exclusion, by treatment arm, is presented in Table 11 and Table 12. A separate table is provided for each disease group and study population.

Listing 1 and Listing 2 will include subjects who discontinued dosing or terminated from study follow-up, and the reason will be included. The listings will be displayed separately for each disease group and study population.

7.2. Protocol Deviations

A summary of subject-specific protocol deviations will be presented by the reason for the deviation, the deviation category, and treatment group for all subjects (Table 8), separately for each disease group and study population. All subject-specific protocol deviations and non-subject-specific protocol deviations will be included as data listings (Listing 3, Listing 4, Listing 5, and Listing 6, respectively).

8. EFFICACY EVALUATION

All efficacy analyses will be performed on the modified Intention-to-Treat (mITT) population, as described in section 4.3.1, as a primary analysis. As a secondary analysis, the analysis will be repeated on the per-protocol population, as described in section 4.3.2. All tests will be two-sided and will use a significance level of 0.05. No adjustments will be made for multiple testing. All results will be reported as point estimates (differences in proportions, odds ratios or mean differences across groups, as appropriate) and interval estimates (95% confidence intervals).

8.1. Primary Efficacy Analysis

8.1.1. Amebiasis Group

For the asymptomatic population, the primary amebiasis endpoint is clearance of Entamoeba histolytica by day 7, defined as no detection of cysts or trophozoites of Entamoeba histolytica or negative antigen detection on day 7. The differences in parasite clearance rates between the placebo and auranofin arms for Entamoeba histolytica will be reported, along with the odds ratio (OR) and their 95% confidence intervals. The confidence interval for the odds ratio will be computed using the assumption of asymptotic normality of the log odds ratio, which should hold in this case as sample sizes are 34 in each arm. The difference in proportions is normally distributed for large enough sample sizes unless one or both of the proportions being estimated is near the boundary of the parameter space (i.e., zero or one). We expect normality to hold as we expect 15-20% parasitological response in the placebo group and 80% in the treatment group, but if it does not, we will use the adjusted Wald estimate as recommended by Agresti and Coull [3].

If some subjects are missing their response value, multiple imputation, as described in section 5 above, will be used to adjust estimates of treatment effect and standard error.

The following hypotheses will be tested:

> H_0: The probability of parasitological response by Day 7 for subjects receiving auranofin is equal to that for those receiving placebo.
>
> H_A: The probability of parasitological response by Day 7 for subjects receiving auranofin differs from that for those receiving placebo.

As a secondary analysis, multivariable logistic regression analysis will be performed to study the association between clearance rates and intervention arm, adjusting for baseline demographic and clinical characteristics. A series of models will compare each baseline covariate with treatment status and the response. Baseline variables will include demographic variables, baseline vital signs and laboratory values. Covariates that are significantly associated with both treatment group and outcome ($p < 0.10$) will be selected as predictors in a multivariable logistic regression model as these are possible confounding variables. The logistic regression model assumes that continuous covariates are linearly related to the log odds of the response. To test this assumption, we will calculate the empirical log odds of the response repeatedly for different observed intervals of the covariate (e.g., calculate the empirical log odds when the covariate is valued 0-5, 5-10, 10-15, etc.), and plot the empirical log odds against the covariate interval. If the linearity assumption holds, this graph will show an approximately linear pattern. Transformations (e.g. the log transformation) for continuous covariates showing a nonlinear relationship to the response will be considered.

Table 18 and Table 20 will present the numbers and proportions (with 95% confidence intervals) of subjects with parasitological response by Day 7 for the treatment and placebo arms in the amebiasis strata for the

asymptomatic and symptomatic populations, respectively. These tables also present the difference in proportions between treatment and placebo groups and odds ratios, with their 95% confidence intervals. Separate versions of the tables will be provided for the modified-Intention-to-Treat population and the Per-Protocol population.

In the symptomatic population, the primary outcome is resolution of diarrhea by Day 7. This variable will be analyzed with the same approach above described for the analysis of parasitological response in the asymptomatic population. The following hypotheses will be tested:

> H_0: The probability of resolution of diarrhea by Day 7 for subjects receiving auranofin is equal to that for those receiving placebo.
>
> H_A: The probability of resolution of diarrhea by Day 7 for subjects receiving auranofin differs from that for those receiving placebo.

8.1.2. Giardiasis Group

The primary endpoint for the giardiasis group is clearance of Giardiasis by day 5, defined as no detections of cysts or trophozoites of Giardia or negative antigen detection on day 5. This endpoint is analogous to the amebiasis endpoint except for the time point, and analogous methods will be applied. Table 19 and Table 21 will present the numbers and proportions (with 95% confidence intervals) of subjects with parasitological response by Day 7 for the treatment and placebo arms in the giardiasis strata for the asymptomatic and symptomatic populations, respective. These tables also present the difference in proportions between treatment and placebo groups and odds ratios, with their 95% confidence intervals. Separate versions of the tables will be provided for the modified-Intention-to-Treat population and the Per-Protocol population.

In the symptomatic population, the primary outcome is resolution of diarrhea by Day 5. This variable will be analyzed with the same approach above described for the analysis of parasitological response.

8.2. Secondary Efficacy Analyses

8.2.1. Amebiasis Group

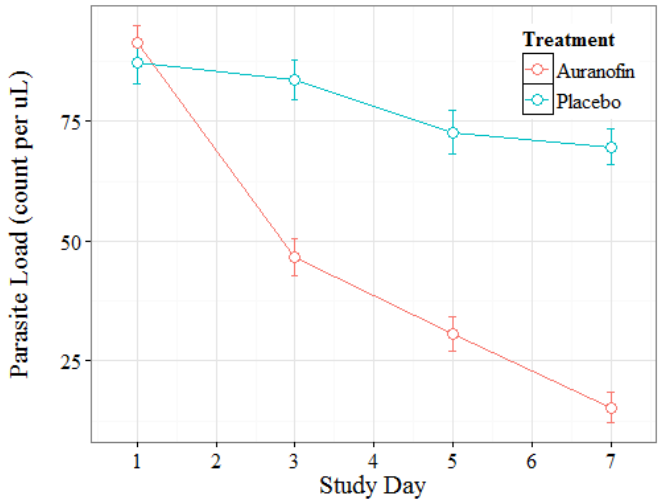
The secondary outcome measures for the asymptomatic amebiasis group are:

1. Parasitological response (no detection of cysts or trophozoites on microscopic exam or negative antigen detection) by Day 3 and 5
2. Rate of decrease of trophozoite/cyst load by qPCR in stools by Days 3,5 and 7
3. Proportion of subjects with negative stool antigen test by Days 3, 5, 7, and 14
4. Proportion of subjects with sustained cure (no detection of cysts or trophozoites by microscopic exam or negative antigen detection) at 14 and 28 days
5. Proportion of subjects with relapse (same strain) or re-infection (new strain) with positive stools at 14 and 28 days by genotyping the initial vs. subsequent strain.

Secondary outcome (1) corresponds to the primary outcome, except that the time points of measurement differ. Therefore, methods perfectly analogous to those used for the primary outcome will be applied to the first secondary outcome. Secondary outcomes (3) – (5) above are also dichotomous, so will be analyzed with methods analogous to those described for the primary outcome (e.g. odds ratios with 95% confidence intervals, and/or logistic regression with confounders included as predictors).

Secondary aim (2) includes the sole numeric outcome (parasite load), and this is measured at multiple time points. For secondary aim (2), a mixed effects model will be used to compare the rate of change in parasite loads between the two study arms. A mixed effects model allows us to incorporate information for multiple time points into a single model while explicitly adjusting for the correlation (due to repeated measures on the same subjects) that naturally arises from this data structure. [4] Below the mixed effects model for the per-protocol analysis is described. This is followed by a description of how the model will be adjusted in the m-ITT population analysis in order to account for missing data.

Parasite load measured on study days 1, 3, 5, and 7 will be included in the mixed effects model. The mean parasite load with 95% confidence intervals will be displayed graphically for each time point for each treatment group, as shown in the example figure below:



If a linear relationship between parasite load and time is observed for both groups, then a model that makes use of this simplifying assumption will be used. Letting *Y* denote parasite load, *t* denote the time point (study day), and *i* be a subject index, and letting *treatment*=1 for those in the treatment group and *treatment*=0 for those in the placebo group, we will model parasite load as:

$$Y_{it} = \beta_0 + \beta_1 t + \mu_i + \alpha_i t + \beta_2 treatment + \beta_3 treatment \cdot t + \epsilon,$$

Note that the above graph does not depict a linear decline in parasite load over time. If the relationship is nonlinear, as depicted in the figure above, then transformation (e.g. log transformation) may be applied, or we will fit the following model, which relaxes the linearity assumption. Let $1_{[t=k]}$ denote an indicator variable taking the value one when t=k and zero otherwise. Let u_i denote the random intercept for subject i, and let α_i denote the random slope for subject i, and assume these random effects are normally distributed with mean zero. Then without assuming linearity, the parasite load for subject i at time t can be modeled as:

$$Y_{it} = \beta_0 + \mu_i + \alpha_i t + \beta_1 \cdot treatment + \beta_2 1_{[t=3]} + \beta_3 1_{[t=3]} \cdot treatment + \beta_4 1_{[t=5]} + \beta_5 1_{[t=5]} \cdot treatment + \beta_4 1_{[t=7]} + \beta_5 1_{[t=7]} \cdot treatment + \epsilon,$$

The error terms, ϵ, are assumed to be independent and normally distributed with constant variance and mean zero. If residual plots indicate that variance is not constant and/or the errors are not normally distributed,

transformations (e.g., the log transformation of the response) will be considered. Choice of covariance structures for the random effects (e.g., compound symmetric and autoregressive), will be explored.

In this model, the expected parasite load for the placebo group on Day 1 is β_0, and on Day 3 (t=3) is $\beta_0 + \beta_2$. Therefore, the expected decrease from time Day 1 to Day 3 is β_2 for the placebo group. The expected parasite load for the treatment group on Day 1 is $\beta_0 + \beta_1$, and on Day 3, it is $\beta_0 + \beta_1 + \beta_2 + \beta_3$. Therefore, the expected decrease for the treatment group from Day 1 to Day 3 is $\beta_2 + \beta_3$. Thus, the difference in rate of decrease of parasite load from Day 1 to Day 3 between treatment and control groups is, on average, β_3. The parameters β_5 and β_7 are interpreted analogously.

The per-protocol analysis will be performed as described above. The per-protocol population, by definition, has no missing data. For the m-ITT analysis, if there is missing outcome data, the model will be altered to adjust for missing response values, which we assume, as previously described, to be missing at random. Covariates that are associated with missingness (p>0.10 via t-test, Fisher's exact test, or chi-square test, as appropriate) will also be included as explanatory variables in the model. This model naturally adjusts for values that are missing at random, so multiple imputation is not required.

The secondary outcomes will be summarized in Table 22 through Table 34. Table 22 and Table 24 will present clearance rates for the amebiasis group with 95% confidence intervals on Days 3, 5, and 7 for the treatment and placebo groups, as well as the differences in clearance rates and 95% confidence intervals for the differences. Table 23 and Table 25 are analogous tables for the giardiasis group. Table 26 will present the coefficient estimates for the mixed effects model for the amebiasis group. Table 27 is the analogous table for the giardiasis group. Table 28 will present the proportion of subjects in the amebiasis group with negative stool antigen test on Days 1, 3, 5, 7, and 14. This outcome is not analyzed for the giardiasis group. Table 29 will present the proportion of subjects with sustained cure for the amebiasis group on days 7, 14, and 28, for each treatment arm, with 95% confidence intervals, as well as the difference in proportions between treatment arms and 95% confidence interval for the difference. Table 30 will present analogous summaries for the giardiasis group (Day 5 instead of Day 7). Table 31 will present the proportion of subjects in the amebiasis group with relapse by Day 14, the proportion with reinfection by Day 14, and the proportion with either relapse or reinfection by Day 14, separately for each treatment arm, with 95% confidence intervals. Table 32 is the analogous table for the giardiasis group. Differences in proportions between treatment arms and 95% confidence intervals for the differences will also be included. Table 33 will present a perfectly analogous summary for Day 28 rather than Day 14, for the amebiasis group. Table 34 is the analogous table for the giardiasis group. Listing 15 and Listing 16 provide a listing for all efficacy endpoints for the amebiasis groups; Listing 17 and Listing 18 are the analogous listings for the giardiasis groups.

The secondary outcomes for the symptomatic population are identical to those for the asymptomatic population with the following exceptions:

- Parasitological response is defined differently, and parasitological response on Day 5 (giardiasis) and Day 7 (amebiasis) were changed from primary to secondary.
- Time to resolution of diarrhea was added as an endpoint.

The outcomes that are identical to the asymptomatic population will be analyzed identically. Parasitological response on Day 5 (giardiasis) and Day 7 (amebiasis) will be analyzed by the methods planned for parasitological response on the other study days, described above. Kaplan-Meier curves and log rank tests will be used to compare time to diarrhea resolution between the treatment and control arm for each disease group (Figure 4).

8.2.2. Giardiasis Group

The secondary outcomes for the asymptomatic giardiasis group are:

6. Parasitological response (no detection of cysts or trophozoites on microscopic exam or negative antigen detection) by Day 3
7. Rate of decrease of trophozoite/cyst load by qPCR in stools by Days 3,5
8. Proportion of subjects with sustained cure (no detection of cysts or trophozoites by microscopic exam or negative antigen detection) at 14 and 28 days
9. Proportion of subjects with relapse (same strain) or re-infection (new strain) with positive stools at 14 and 28 days by genotyping the initial vs. subsequent strain

These outcomes are analogous to the asymptomatic amebiasis outcomes and will be analyzed using perfectly analogous methods.

Similarly, the secondary outcomes for the symptomatic giardiasis population will be analyzed analogously to those for the symptomatic amebiasis population

9. SAFETY EVALUATION

9.1. Demographic and Other Baseline Characteristics

Summaries of age, sex, ethnicity, and race will be presented by treatment group and overall (Table 15 and Table 16), for each disease group and study population. Ethnicity is categorized as "Hispanic or Latino", or "Not Hispanic or Latino". In accordance with NIH reporting policy, subjects may self-designate as belonging to more than one race or may refuse to identify a race, the latter reflected in the CRF as "No" to each racial option.

Individual subject listings will be presented for all demographics (Listing 9 and Listing 10); pre-existing medical conditions (Listing 11 and Listing 12); vital signs and oral temperature (Listing 31 and Listing 32); and concomitant medications (Listing 35 and Listing 36). These listings will be presented separately for each disease group and study population.

9.1.1. Prior and Concurrent Medical Conditions

All current illnesses and past pre-existing medical conditions will be MedDRA coded using MedDRA dictionary version 18.1 or higher. Summaries of subjects' pre-existing medical conditions will be presented by treatment group (Table 17), disease group, and study population. Individual subject listings will be presented for all medical conditions (Table 11 and Table 12). Listings are presented separately for each disease group and study population.

9.1.2. Prior and Concomitant Medications

Summaries of medications that were started prior to dosing and continuing at the time of dosing will be presented by WHO Drug classification and treatment group, separately for each disease group and study population (Table 79 and Table 80). Individual subject listings will be presented for all concomitant medications (Listing 35 and Listing 36).

9.2. Measurements of Treatment Compliance

In the amebiasis group, all subjects were to receive a total of 7 doses of study product (once a day for 7 days). In the giardiasis group, all subjects were to receive a total of 5 doses of study product (once a day for 5 days). The number of doses of study product administered to subjects will be presented by treatment group as part of the subject disposition tables, separately for each disease group and study population (Table 9 and Table 10). Listing 13 and Listing 14 list the doses missed and treatment assignment for each subject.

Table 13 summarizes dosing dates by treatment arm, disease group, and study population.

9.3. Adverse Events

9.3.1. Solicited Events and Symptoms

Adverse event data is collected at each visit using specific questions and/or targeted physical examination. Based on the adverse reactions that have been observed with the use of auranofin in previous studies, the following solicited events are tracked: loose stools or diarrhea, abdominal pain, nausea with or without vomiting, constipation, anorexia, flatulence, dyspepsia, dysgeusia, pruritus, hair loss, urticaria, stomatitis, conjunctivitis, glossitis, hematuria, and rash. Hematologic, renal, or hepatic laboratory abnormalities are

picked up on testing at day 7. Adverse event collection continues until Day 28 (following three half-lives of the drug). As the drug is administered orally, no local event reactivity is recorded.

Table 35 and Table 36 display the number, percentage, and 95% confidence interval for the percentage of subjects experiencing each solicited adverse event, by treatment group, separately for the amebiasis group and the giardiasis group. Solicited adverse events are also displayed graphically. Figure 5 displays the maximum severity of solicited symptoms per subject by day post treatment, for each treatment group and for both treatment groups combined, separately for each disease group and study population.

Solicited systemic events by subject will be presented in Listing 19, Listing 20, Listing 21, and Listing 22.

9.3.2. Unsolicited Adverse Events

Unsolicited adverse events will be coded to a Medical Dictionary for Regulatory Activities Terminology (MedDRA) version 18.1 or later. Adverse Events will be summarized using the number and percentage of subjects who experienced each event overall for the safety population. When calculating the incidence of adverse events (i.e., on a per subject basis), each subject will only be counted once for each PT and SOC and any repetitions of adverse events within a subject for a PT or SOC will be ignored; the denominator will be the total number of subjects in the safety population. All adverse events reported will be included in the summaries and analyses.

Table 37 through Table 40 summarize the number and percentage of subjects experiencing unsolicited adverse events by MedDRA System Organ Class and Preferred Term, severity, and relationship, by treatment, disease group, and study population.

A listing of serious adverse events, sorted by study population, disease group, and treatment group, is presented in Table 41. Listings of non-serious, unsolicited, moderate or severe adverse events, separately for each disease group and study population, are presented in Table 42 and Table 43.

Unsolicited adverse events are also displayed graphically. Figure 6 and Figure 7 display the frequency of unsolicited adverse events by MedDRA System Organ Class by treatment group, separately for each disease group and study population. Figure 8 and Figure 9 display the incidence of adverse events by MedDRA System Organ Class by treatment group, separately for each disease group and study population. Figure 10 and Figure 11 summarize the frequency of unsolicited adverse events by severity for each treatment group and overall, separately for each disease group and study population. Figure 12 and Figure 13 display the incidence of unsolicited adverse events by severity for each treatment group and overall, separately for each disease group and study population. Figure 14 and Figure 15 display the frequency of unsolicited adverse events by MedDRA System Organ Class and relationship to treatment, by treatment group, separately for each disease group and study population. Figure 16 and Figure 17 display the incidence of unsolicited adverse events by MedDRA System Organ Class and relationship to treatment, by treatment group, separately for each disease group and study population. Figure 18 and Figure 19 display the frequency of unsolicited adverse events by relationship to treatment, by treatment group, separately for each disease group and study population. Figure 20 and Figure 21 display the incidence of unsolicited adverse events by relationship to treatment, by treatment group, separately for each disease group and study population.

Unsolicited adverse events by subject will be presented in Listing 23 and Listing 24, separately for each disease group and study population.

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

Section 14.3.3 will include narratives of deaths, and other serious and significant adverse events.

9.5. Pregnancies

Auranofin is a Category C drug whose use is not recommended in pregnant women because of studies in pregnant rabbits and rats with decreased maternal and fetal weight and litter size with 4-50X the human daily dose. This trial excludes pregnant women based on a pregnancy test during screening and requires two forms of contraception for the length of the trial (5-7 days) and for three half-lives of the drug (total 4 months). For any subjects in the Safety population who became pregnant during the study, study medication was stopped. Every attempt will be made to follow these subjects to completion of pregnancy to document the outcome, including information regarding any complications with pregnancy and/or delivery. A listing of pregnancies and outcomes will be presented (Listing 37 through Listing 41).

9.6. Clinical Laboratory Evaluations

Laboratory parameters include white blood cell count, hemoglobin, hematocrit, platelets, BUN, Creatinine, AST, ALT, and urine protein, all measured during screening and on Study Day 7. Units and severity grading for the labs are summarized in Table 7.

The distribution of laboratory results by maximum severity, study day and treatment group will be presented, separately for each disease group and study population, in Table 46 through Table 50. Abnormal laboratory results related to study treatment will be summarized by maximum severity, study day, and treatment group in Table 51 through Table 58, separately by disease group and study population. Descriptive statistics including mean, standard deviation, median, minimum and maximum values by study day, for each laboratory parameter, will be summarized separately for each disease group and study population in Table 59 through Table 66. Note that in general, summaries include only scheduled labs: unscheduled follow-up labs will be excluded from summaries but included in the listings. These include summaries at each time point as well as summaries in the change in observed values from baseline to Day 7. Listings of abnormal laboratory events (one listing for each disease group and study population) will be included in Table 44 and Table 45. Time trends of laboratory values will be graphically displayed in Figure 22 and Figure 23. Listings for all laboratory values will be provided, separately for each disease group and study population, in Listing 25 through Listing 30.

9.7. Vital Signs and Physical Evaluations

Vital signs include height and weight, temperature, systolic and diastolic blood pressure, and pulse. These were assessed during screening and on every scheduled visit. Targeted physical exams were conducted on the same days and looked for abdominal pain, hair loss, urticaria, rashes, stomatitis, conjunctivitis, and glossitis. Refer to Table 6 for vital sign grading criteria.

Vital signs will be tabulated by visit, severity, and treatment group, separately for each disease group and study population (Table 67 through Table 78). Vital sign listings will be provided for subjects in the Safety population (Listing 31 and Listing 32). Physical exam findings will be listed in Listing 33 and Listing 34.

9.8. Concomitant Medications

Concomitant medications will be coded to the Anatomical Therapeutic Classification using the WHO Drug Dictionary. The use of prior and concomitant medications taken during the study will be recorded on the CRFs. A by-subject listing of concomitant medication use will be presented (Listing 35 and Listing 36). The use of concomitant medications during the study will be summarized by WHO drug classification and treatment group, separately for each disease group and study population, for the Safety population (Table 79 and Table 80).

10. PHARMACOKINETICS

Not applicable.

11. IMMUNOGENICITY

Not applicable.

12. OTHER ANALYSES

Not applicable.

13. REPORTING CONVENTIONS

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Proportions will be presented as two decimal places; values <0.01 will be presented as "<0.01". Percentages will be reported to the nearest whole number; values <1% will be presented as "<1". Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

14. TECHNICAL DETAILS

SAS version 9.4 or above and/or R version 3.2.2 or above will be used to generate all tables, figures and listings and perform statistical analyses.

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

Version 2.0 of the Statistical Analysis Plan incorporates the following updates:

- Updated description of design to add symptomatic population and new site. These were added in protocol updates since the first version of the SAP.
- Endpoints and analysis plans for symptomatic population were added.
- Updated definition of mITT and PP analysis populations to handle unanticipated enrollment of participants who did not test positive for the disease.
- Updated eligibility criteria and grading ranges based on protocol updates.
- Updated covariance structure options for mixed effects model to facilitate comparison between mITT and PP populations.
- Added possibility of transformation (e.g. log transformation) of response for mixed effects model to attain better fit.
- Removed tables summarizing solicited events by symptom, treatment group, day, and severity and unsolicited adverse events by MedDRA SOC and PT, treatment group, and day, because this level of granularity is not needed for the small numbers of events that have been observed.
- Replaced change from baseline plots for lab parameters with time trend plots displaying grading ranges.
- Removed analysis plans relating to Versions 1.0-3.0 of the protocol since the earliest subjects enrolled under Version 4.0.

16. REFERENCES

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4. Diggle, Peter, Patrick Heagerty, Kung-Yee Liang, and Scott Zeger. *Analysis of longitudinal data*. OUP Oxford, 2013.
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17. LISTING OF TABLES, FIGURES, AND LISTINGS

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

APPENDICES

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

10.2 Protocol Deviations

Table 8: Distribution of Protocol Deviations by Category, Type, and Treatment Group, Asymptomatic Population

This table will be repeated for the symptomatic population.

Category	Deviation Type	Amebiasis Group, Auranofin, 6 mg (N=34)		Amebiasis Group, Placebo (N=34)		Giardiasis Group, Auranofin, 6 mg (N=34)		Giardiasis Group, Placebo (N=34)		All Subjects (N=136)	
		# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.
Eligibility/enrollment	Any type	x	x	x	x	x	x	x	x	x	x
	Did not meet inclusion criterion										
	Met exclusion criterion										
	ICF not signed prior to study procedures										
	Other										
Treatment administration schedule	Any type										
	Out of window visit										
	Missed visit/visit not conducted										
	Missed treatment administration										
	Delayed treatment administration										
	Other										
Follow-up visit schedule	Any type										
	Out of window visit										
	Missed visit/visit not conducted										
	Other										
Protocol procedure/assessment	Any type										

Table 8: Distribution of Protocol Deviations by Category, Type, and Treatment Group, Asymptomatic Population *(continued)*

Category	Deviation Type	Amebiasis Group, Auranofin, 6 mg (N=34)		Amebiasis Group, Placebo (N=34)		Giardiasis Group, Auranofin, 6 mg (N=34)		Giardiasis Group, Placebo (N=34)		All Subjects (N=136)	
		# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.
	Incorrect version of ICF signed										
	Blood not collected										
	Urine not collected										
	Stool not collected										
	Other specimen not collected										
	Too few aliquots obtained										
	Specimen result not obtained										
	Required procedure not conducted										
	Required procedure done incorrectly										
	Study product temperature excursion										
	Specimen temperature excursion										
	Other										
Treatment administration	Any type										
	Required procedure done incorrectly										
	Study product temperature excursion										
	Other										
Blinding policy/procedure	Any type										

Table 8: Distribution of Protocol Deviations by Category, Type, and Treatment Group, Asymptomatic Population *(continued)*

Category	Deviation Type	Amebiasis Group, Auranofin, 6 mg (N=34)		Amebiasis Group, Placebo (N=34)		Giardiasis Group, Auranofin, 6 mg (N=34)		Giardiasis Group, Placebo (N=34)		All Subjects (N=136)	
		# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.
	Treatment Unblinded										
	Other										

14.1 Description of Study Subjects

14.1.1 Disposition of Subjects

Table 9: Subject Disposition by Treatment Group, Amebiasis Group, Asymptomatic Population

This table will be repeated for the symptomatic population.

Subject Disposition	Auranofin, 6 mg (N=X)		Placebo (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%
Screened	x	x.x	x	x.x	x	x.x
Enrolled and Received Treatment						
Received dose 1						
Received dose 2						
Received dose 3						
Received dose 4						
Received dose 5						
Received dose 6						
Received dose 7						
Received All Scheduled Doses [a]						
Completed Final Stool Sample (Day 7)						
Completed Follow-up (Study Day 28)[a]						
Completed Per Protocol[b]						

[a]Refer to Listing 16.2.1 for reasons subjects discontinued or terminated early.
[b]Refer to Listing 16.2.2.1 for protocol deviations and Listing 16.2.3 for reasons subjects are excluded from the per protocol population.

Table 10: Subject Disposition by Treatment Group, Giardiasis Group, Asymptomatic Population

This table will be repeated for the symptomatic population.

Subject Disposition	Auranofin, 6 mg (N=X)		Placebo (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%
Screened	x	x.x	x	x.x	x	x.x
Enrolled and Received Treatment						
Received dose 1						
Received dose 2						
Received dose 3						
Received dose 4						
Received dose 5						
Received All Scheduled Doses [a]						
Completed Final Stool Sample (Day 7)						
Completed Follow-up (Study Day 28)[a]						
Completed Per Protocol[b]						

[a]Refer to Listing 16.2.1 for reasons subjects discontinued or terminated early.
[b]Refer to Listing 16.2.2.1 for protocol deviations and Listing 16.2.3 for reasons subjects are excluded from the per protocol population.

Table 11: Analysis Populations by Treatment Group, Amebiasis Group, Asymptomatic Population

This table will be repeated for the symptomatic population.

Analysis Populations	Reason Subjects Excluded	Auranofin (N=X)		Placebo (N=X)		All Subjects (N=X)	
		n	%	n	n	%	n
Modified Intent to Treat Population	Did not receive study product	x	x.x	x	x.x	x	x.x
Per-Protocol Population	Any Reason						
	Missed one or more doses of study product						
	Out-of-window dose						
	Out-of-window endpoint						
	[Other reasons may be specified]						
Safety Population	Any Reason						
	[Reason 1]						
	[Reason 2]						

Table 12: Analysis Populations by Treatment Group, Giardiasis Group

Table will be formatted as Table 11.
This table will be repeated for the symptomatic population.

Table 13: Dates of First Treatment by Disease Group and Treatment Group, Asymptomatic Population

This table will be repeated for the symptomatic population.

Dates of Dosing	Amebiasis Group, Auranofin, 6 mg (N=X)	Amebiasis Group, Placebo (N=X)	Giardiasis Group, Auranofin, 6 mg (N=X)	Giardiasis Group, Placebo (N=X)	All Subjects (N=X)
DDMMMYYYY-DDMMMYYYY [categorize based on length of enrollment period]	x	x	x	x	x
Total					

Table 14: Ineligibility Summary of Screen Failures, Asymptomatic Population

This table will be repeated for the symptomatic population, which had different inclusion and exclusion criteria.

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	Number of Times Item Marked Ineligible*
Inclusion and Exclusion	Number of subjects failing any eligibility criterion	x
Inclusion	Provide written informed consent prior to initiation of any study procedures.	x
Inclusion	Able to understand and comply with planned study procedures and be available for all study visits.	x
Inclusion	Male or non-pregnant female 18-65 years of age, inclusive.	x
Inclusion	Amebiasis or giardiasis identified by positive Tech Lab antigen test, positive wet mount or trichome (confirmed by PCR), or positive stool PCR for *E. histolytica* or *Giardia*. If a subject is infected with both *E. histolytica* and *Giardia,* they will be enrolled in the *E. histolytica* study arm. Once the *Entamoeba* study arm is fully enrolled, any subsequent dual infected subjects will be enrolled in the *Giardia* arm. .	x
Inclusion	In otherwise good health.[1]	x
Inclusion	Vital signs (oral temperature, pulse, and blood pressure) are all within normal protocol-defined ranges.	x
Inclusion	Laboratory tests (blood urea nitrogen, creatinine, AST, ALT, white blood cells, platelets, hemoglobin, and hematocrit) are all within normal protocol-defined reference ranges.[2]	x

[1] As determined by medical history and targeted physical examination, if indicated based on medical history, to evaluate acute or currently ongoing chronic medical diagnoses or conditions that would affect the assessment of eligibility and safety of subjects. Existing medical diagnoses or conditions except those in the Subject Exclusion Criteria) must be deemed as stable chronic medical conditions. A stable chronic medical condition is defined as no change in prescription medication, dose, or frequency of medication in the last 3 months (90 days) and health outcomes of the specific disease are considered to be within acceptable limits in the last 6 months (180 days). Any *change due to change of health care provider, insurance company, or that is done for financial reasons, as long as in the same* class of medication, will not be considered a violation of this inclusion criterion. Any change in prescription medication due to **improvement** of a disease outcome, as determined by the site principal investigator or appropriate sub-investigator, will not be considered a violation of this inclusion criterion. Subjects may be on chronic or as needed (prn) medications if, in the opinion of the site principal investigator or appropriate sub-investigator, they pose no additional risk to subject safety. *Topical, nasal, and inhaled medications, vitamins, and contraceptives are permitted.*

[2] The normal protocol-defined ranges for laboratory tests include (a) blood urea nitrogen (BUN) between 5 and 24 mg/dL, inclusive, (b) creatinine between 53 and 106 umol/L, inclusive, males and between 44 and 97umol/L, inclusive, for females, (c) AST of 38 U/L or less for males and 32 U/L or less for females, (d) ALT of 41.0 U/L or lessor males and 31 U/L or less for females, (e) WBC between 3.5 and 11.0 10^9/L, inclusive, (f) platelets between 150 and 450 10^9/L, inclusive, (g) hemoglobin between 12.5 and 17.5 gm/dL, inclusive, for males and 11.5 and 16.5 gm/dL,

Table 14: Ineligibility Summary of Screen Failures, Asymptomatic Population *(continued)*

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	Number of Times Item Marked Ineligible*
Inclusion	Urinalysis with no greater than trace protein. If a high protein is confirmed to be due to menstruation, it should be repeated	x
Inclusion	Women of reproductive potential[3] must have a negative urine pregnancy test within 72 hours of starting study medications.	x
Inclusion	Female subjects who are participating in sexual activity that could lead to pregnancy must agree to use highly effective[4] contraception plus condoms while receiving auranofin and for 15 weeks after. These will be supplied to female subjects while they are on the trial and for the follow-up period of 4 months total. Females on effective forms of birth control will continue while on the study and for the follow-up period of 4 months total.	x
Exclusion	Known intolerance of auranofin or gold compounds.	x
Exclusion	Pregnant or breastfeeding women or women who plan to become pregnant or breastfeed at any given time during the study or within 2 months of study completion.	x
Exclusion	Diarrhea (> 3 loose stools/ 24 hours) within 7 days prior to starting study medications.	x
Exclusion	Anticipated travel of more than 50 km from study site planned in next month.	x
Exclusion	Evidence of clinically significant renal, hepatic, or immunologic impairment.[5]	x
Exclusion	Current use of systemic antibiotics or metronidazole.	x

inclusive, for females, (h) hematocrit between 40.0 and 52.0%, inclusive, for males and 35.0 and 47.0%, inclusive, for females. Subjects with low BUN or creatinine will be allowed to enroll, as it is not of clinical significance.

[3] Female subjects who are surgically sterile via tubal sterilization, bilateral oophorectomy or hysterectomy or who have been postmenopausal for greater than 1 year are not considered to be of reproductive potential.

[4] Highly effective methods of contraception are defined as having low failure rates (i.e. less than 1% per year) when used consistently and correctly and may include, but are not limited to, abstinence from intercourse, monogamous relationship with a vasectomized partner, male condoms or diaphragm with spermicide, intrauterine devices, and licensed hormonal methods.

[5] Renal: Creatinine >1.5 mg/dL, Blood urea nitrogen >30 mg/dL, or urine dipstick 1+ protein; Hepatic: AST or ALT >60 U/L; Immunologic: White blood cells < 4.0 (10^9/L), Platelets < 100 (10^6/L), or Hemoglobin <11 gm/dL, Hematocrit <30%

Table 14: Ineligibility Summary of Screen Failures, Asymptomatic Population *(continued)*

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	Number of Times Item Marked Ineligible*
Exclusion	Has any condition that would, in the opinion of the site investigator, place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol.	x
Exclusion	Concurrent participation in other investigational protocols or receipt of an investigational product within the previous 30 days.	x
Exclusion	History of alcohol or drug abuse within the last five years.	X
Exclusion	Current use of systemic antibiotics or metronidazole.	x
*More than one criterion may be marked per subject.		

14.1.2 Demographic Data by Study Group

Table 15: Distribution of Sex, Ethnicity, and Race by Treatment Group, Asymptomatic Population

This table will be repeated for the symptomatic population, but will also split out the summaries by site.

Demographic Category	Characteristic	Amebiasis Group, Auranofin, 6 mg (n=34)		Amebiasis Group, Placebo (n=34)		Amebiasis Group, All subjects (n=68)		Giardiasis Group, Auranofin, 6 mg (n=34)		Giardiasis Group, Placebo (n=34)		Giardiasis Group, All subjects (n=68)		All subjects (n=136)	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%
Sex	Male	x	x.x												
	Female														
Ethnicity	Not Hispanic or Latino														
	Hispanic or Latino														
	Not Reported														
Race	Unknown														
	American Indian or Alaska Native														
	Asian														
	Native Hawaiian or Other Pacific Islander														
	Black or African American														
	White														
	Multi-Racial														
	Unknown														

Table 16: Age Statistics (in Years) by Disease Group and Treatment Group, Asymptomatic Population

This table will be repeated for the symptomatic population, but will also split out the summaries by site.

Variable	Statistic	Amebiasis Group, Auranofin, 6 mg (n=34)	Amebiasis Group, Placebo (n=34)	Amebiasis Group, All subjects (n=68)	Giardiasis Group, Auranofin, 6 mg (n=34)	Giardiasis Group, Placebo (n=34)	Giardiasis Group, All subjects (n=68)	All subjects (n=136)
Age	Mean	x.x	x.x	x.x				
	Standard Deviation	x.x	x.x	x.x				
	Median	x.x	x.x	x.x				
	Minimum	x	x	x				
	Maximum	x	x	x				

14.1.3 Prior and Concurrent Medical Conditions

Table 17: Distribution of Subjects with Pre-Existing Medical Conditions by MedDRA System Organ Class, Disease Group, and Treatment Group, Asymptomatic Population

This table will be repeated for the symptomatic population.

	Amebiasis Group						Giardiasis Group			All Subjects, (both disease groups) (N=X)
	Auranofin, 6 mg (N=X)		Placebo (N=X)		All Subjects (N=X)		Auranofin, 6 mg (N=X)	Placebo (N=X)	All Subjects (N=X)	
MedDRA System Organ Class	n	%	n	%						
Any SOC	x	x.x	x	x.x						
[SOC 1]										
[SOC 2]										
Note: This table presents number and percentage of subjects. A subject is only counted once per SOC.										

Section 14.2 Efficacy Data

Table 18: Comparison of Clearance Rates between Auranofin Group and Placebo Group, Day 7 (primary endpoint), Amebiasis Group, Asymptomatic Population

	Number of Subjects	Number with Parasitological Response by Day 7	Clearance Rate (proportion with parasitological response) by Day 7 with 95% CI	Difference in Clearance Rate between Auranofin and Placebo with 95% CI	Odds Ratio with 95% CI	Adjusted Odds Ratio with 95% CI	P-value from Fisher's exact test
Auranofin, 6 mg							
Placebo							
For the asymptomatic population, parasitological response is defined as no detection of cysts or trophozoites by microscopic exam or negative antigen detection. Note: These analyses will be performed both on the m-ITT population and the per-protocol population. Footnote 1: The method for CI calculation will be denoted here. A footnote will list the covariates that were included in the model for the adjusted odds ratio.							

Table 19: Comparison of Clearance Rates between Auranofin Group and Placebo Group, Day 5 (primary endpoint), Giardiasis Group, Asymptomatic Population

	Number of Subjects	Number with Parasitological Response by Day 5	Clearance Rate (proportion with parasitological response) by Day 5 with 95% CI	Difference in Clearance Rate between Auranofin and Placebo with 95% CI	Odds Ratio with 95% CI	Adjusted Odds Ratio with 95% CI	P-value from Fisher's exact test
Auranofin, 6 mg							
Placebo							
For the asymptomatic population, parasitological response is defined as no detection of cysts or trophozoites by microscopic exam or negative antigen detection. Note: These analyses will be performed both on the m-ITT population and the per-protocol population. Footnote 1: The method for CI calculation will be denoted here. A footnote will list the covariates that were included in the model for the adjusted odds ratio.							

Table 20: Comparison of Resolution of Diarrhea between Auranofin Group and Placebo Group, Day 7 (primary endpoint), Amebiasis Group, Symptomatic Population

	Number of Subjects	Number with Resolution of Diarrhea Day 7	Proportion with Resolution of Diarrhea by Day 7 with 95% CI	Difference in proportions with 95% CI	Odds Ratio with 95% CI	Adjusted Odds Ratio with 95% CI	P-value from Fisher's exact test
Auranofin, 6 mg							
Placebo							
Note: These analyses will be performed both on the m-ITT population and the per-protocol population. Footnote 1: The method for CI calculation will be denoted here. A footnote will list the covariates that were included in the model for the adjusted odds ratio.							

Table 21: Comparison of Resolution of Diarrhea between Auranofin Group and Placebo Group, Day 5 (primary endpoint), Giardiasis Group, Symptomatic Population

	Number of Subjects	Number with Resolution of Diarrhea Day 5	Proportion with Resolution of Diarrhea by Day 5 with 95% CI	Difference in proportions with 95% CI	Odds Ratio with 95% CI	Adjusted Odds Ratio with 95% CI	P-value from Fisher's exact test
Auranofin, 6 mg							
Placebo							
Note: These analyses will be performed both on the m-ITT population and the per-protocol population. Footnote 1: The method for CI calculation will be denoted here. A footnote will list the covariates that were included in the model for the adjusted odds ratio.							

Table 22: Comparison of Clearance Rates between Auranofin Group and Placebo Group, Asymptomatic Amebiasis Group

		Clearance rate (proportion with parasitological response) by the specified day (95% CI)		
	Number of Subjects	Day 3	Day 5	Day 7
Auranofin, 6 mg				
Placebo				
Difference in clearance rates (95% CI)				

Note: These analyses will be performed both on the m-ITT population and the per-protocol population.
In the asymptomatic population, parasitological response is defined as no detection of cysts or trophozoites by microscopic exam or negative antigen detection.
Footnote 1: The method for CI calculation will be denoted here.

Table 23: Comparison of Clearance Rates between Auranofin Group and Placebo Group, Asymptomatic Giardiasis Group

		Clearance rate (proportion with parasitological response) by the specified day (95% CI)	
	Number of Subjects	Day 3	Day 5
Auranofin, 6 mg			
Placebo			
Difference in clearance rates (95% CI)			

Note: These analyses will be performed both on the m-ITT population and the per-protocol population.
In the asymptomatic population, parasitological response is defined as no detection of cysts or trophozoites by microscopic exam or negative antigen detection.
Footnote 1: The method for CI calculation will be denoted here

Table 24: Comparison of Clearance Rates between Auranofin Group and Placebo Group, Symptomatic Amebiasis Group

		Clearance rate (proportion with parasitological response) by the specified day (95% CI)		
	Number of Subjects	Day 3	Day 5	Day 7
Auranofin, 6 mg				
Placebo				
Difference in clearance rates (95% CI)				

Note: These analyses will be performed both on the m-ITT population and the per-protocol population.
In the symptomatic population, parasitological response is defined as no detection of trophozoites by microscopic exam.
Footnote 1: The method for CI calculation will be denoted here.

Table 25: Comparison of Clearance Rates between Auranofin Group and Placebo Group, Symptomatic Giardiasis Group

		Clearance rate (proportion with parasitological response) by the specified day (95% CI)	
	Number of Subjects	Day 3	Day 5
Auranofin, 6 mg			
Placebo			
Difference in clearance rates (95% CI)			

Note: These analyses will be performed both on the m-ITT population and the per-protocol population.
In the symptomatic population, parasitological response is defined as no detection of trophozoites by microscopic exam.
Footnote 1: The method for CI calculation will be denoted here

Table 26: Mixed Effects Model Coefficient Estimates, Asymptomatic Amebiasis Group

Coefficient	Estimate	Standard Error	P-value
β_0: Intercept			
β_1: Treatment			
β_2: Day 3			
β_3: Day 3 * Treatment			
β_4: Day 5			
β_5: Day 5 * Treatment			
β_6: Day 7			
β_7: Day 7 * Treatment			
Note: These analyses will be performed both on the m-ITT population and the per-protocol population.			

Table will be repeated for the symptomatic population

.

Table 27: Mixed Effects Model Coefficient Estimates, Asymptomatic Giardiasis Group

Coefficient	Estimate	Standard Error	P-value
β_0: Intercept			
β_1: Treatment			
β_2: Day 3			
β_3: Day 3 * Treatment			
β_4: Day 5			
β_5: Day 5 * Treatment			
Note: These analyses will be performed both on the m-ITT population and the per-protocol population.			

Table will be repeated for the symptomatic population.

Table 28: Comparison of Proportion of Subjects with Negative Stool Antigen Test between Auranofin Group and Placebo Group, Asymptomatic Amebiasis Group

		Proportion with negative stool antigen tests (95% CI) on the specified day					
	Number of Subjects	During Screening	Day 1	Day 3	Day 5	Day 7	Day 14
Auranofin, 6 mg							
Placebo							
Difference in clearance rates (95% CI)							
Note: These analyses will be performed both on the m-ITT population and the per-protocol population. Footnote 1: The method for CI calculation will be denoted here.							

Table will be repeated for the symptomatic population

Table 29: Comparison of Proportion of Subjects with Sustained Cure between Auranofin Group and Placebo Group, Asymptomatic Amebiasis Group

		Proportion with sustained cure on the specified day and 95% CI		
	Number of Subjects	Day 7	Day 14	Day 28
Auranofin, 6 mg				
Placebo				
Difference in clearance rates (95% CI)				
The following definitions are for the asymptomatic amebiasis group: ***Sustained cure on Day 14*** is defined as no detection of cysts or trophozoites on microscopic exam or negative antigen detection on Days 7 and 14. ***Sustained cure on Day 28*** is defined to be no detection of cysts or trophozoites on microscopic exam or negative antigen detection on Days 7, 14, and 28. **Note: These analyses will be performed both on the m-ITT population and the per-protocol population.** Footnote 1: The method for CI calculation will be denoted here.				

Table will be repeated for the symptomatic population.

Footnotes for the repeat table:

Sustained cure on Day 14 *is defined to be no detection of trophozoites on microscopic exam on Days 7 and 14.*
Sustained cure on Day 28 *is defined to be no detection of trophozoites on microscopic exam on Days 7, 14, and 28.*

Table 30: Comparison of Proportion of Subjects with Sustained Cure between Auranofin Group and Placebo Group, Asymptomatic Giardiasis Group

		Proportion with sustained cure on the specified day and 95% CI		
	Number of Subjects	Day 5	Day 14	Day 28
Auranofin, 6 mg				
Placebo				
Difference in clearance rates (95% CI) for the difference				

The following definitions are for the asymptomatic giardiasis group:
Sustained cure on Day 14 is defined to be no detection of cysts or trophozoites on microscopic exam or negative antigen detection on Days 5 and 14.
Sustained cure on Day 28 is defined to be no detection of cysts or trophozoites on microscopic exam or negative antigen detection on Days 5, 14, and 28.
Note: These analyses will be performed both on the m-ITT population and the per-protocol population.
Footnote 1: The method for CI calculation will be denoted here.

Table will be repeated for the symptomatic population.

Footnotes for the repeat table:
Sustained cure on Day 14 *is defined to be no detection of trophozoites on microscopic exam on Days 5 and 14.*
Sustained cure on Day 28 *is defined to be no detection of trophozoites on microscopic exam on Days 5, 14, and 28.*

Table 31: Comparison of Proportion of Subjects with Relapse (Same Strain), and/or Reinfection (Different Strain) by Day 14, - Asymptomatic Amebiasis Group

	Number of Subjects	Proportion with Relapse by Day 14 (95% CI)	Proportion with Reinfection by Day 14 (95% CI)	Proportion with Relapse and/or Reinfection by Day 14 (95% CI)
Auranofin, 6 mg				
Placebo				
Difference in clearance rates (95% CI)				
Note: These analyses will be performed both on the m-ITT population and the per-protocol population. Footnote 1: The method for CI calculation will be denoted here.				

Table 32: Comparison of Proportion of Subjects with Relapse (Same Strain), and/or Reinfection (Different Strain) by Day 14, - Asymptomatic Giardiasis Group

	Number of Subjects	Proportion with Relapse by Day 14 (95% CI)	Proportion with Reinfection by Day 14 (95% CI)	Proportion with Relapse and/or Reinfection by Day 14 (95% CI)
Auranofin, 6 mg				
Placebo				
Difference in clearance rates (95% CI)				
Note: These analyses will be performed both on the m-ITT population and the per-protocol population. Footnote 1: The method for CI calculation will be denoted here.				

Tables will be repeated for the symptomatic population.

Table 33: Comparison of Proportion of Subjects with Relapse (Same Strain), and/or Reinfection (Different Strain) by Day 28, - Asymptomatic Amebiasis Group

	Number of Subjects	Proportion with Relapse by Day 28 (95% CI)	Proportion with Reinfection by Day 28 (95% CI)	Proportion with Relapse and/or Reinfection by Day 28 (95% CI)
Auranofin, 6 mg				
Placebo				
Difference in clearance rates (95% CI)				
Note: These analyses will be performed both on the m-ITT population and the per-protocol population. Footnote 1: The method for CI calculation will be denoted here.				

Table 34: Comparison of Proportion of Subjects with Relapse (Same Strain), and/or Reinfection (Different Strain) by Day 28, - Asymptomatic Giardiasis Group

	Number of Subjects	Proportion with Relapse by Day 28 (95% CI)	Proportion with Reinfection by Day 28 (95% CI)	Proportion with Relapse and/or Reinfection by Day 28 (95% CI)
Auranofin, 6 mg				
Placebo				
Difference in clearance rates (95% CI)				
Note: These analyses will be performed both on the m-ITT population and the per-protocol population. Footnote 1: The method for CI calculation will be denoted here				

Tables will be repeated for the symptomatic population.

14.3 Safety Data

14.3.1 Displays of Adverse Events

14.3.1.1 Solicited Adverse Events

Table 35: Number and Percentage of Subjects Experiencing Solicited Events with 95% Confidence Intervals by Symptom and Treatment Group, - Asymptomatic Amebiasis Group

	Auranofin, 6 mg (N=X)			Placebo (N=X)		
Symptom	n	%	95% CI	n	%	95% CI
Any Symptom	x	x.x	x.x, x.x	x	x.x	x.x, x.x
Loose stools or diarrhea						
Abdominal Pain						
Nausea with or without vomiting						
Constipation						
Anorexia						
Flatulence						
Dyspepsia						
Dysgeusia						

Table 35: Number and Percentage of Subjects Experiencing Solicited Events With 95% Confidence Intervals by Symptom and Treatment Group, - Asymptotic Amebiasis Group *(continued)*

Symptom	Auranofin, 6 mg (N=X)			Placebo (N=X)		
	n	%	95% CI	n	%	95% CI
Pruritus						
Hair loss						
Urticaria						
Stomatitis						
Conjunctivitis						
Glossitis						
Hematuria						
Rash						

Table will be repeated for the symptomatic study population but will exclude loose stools or diarrhea.

Table 36: Number and Percentage of Subjects Experiencing Solicited Events with 95% Confidence Intervals by Symptom and Treatment Group, Asymptomatic Giardiasis Group

	Auranofin, 6 mg (N=X)			Placebo (N=X)		
Symptom	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Any Symptom	x	x.x	x.x, x.x	x	x.x	x.x, x.x
Loose stools or diarrhea						
Abdominal Pain						
Nausea with or without vomiting						
Constipation						
Anorexia						
Flatulence						
Dyspepsia						
Dysgeusia						
Pruritus						
Hair loss						
Urticaria						

Table 36: Number and Percentage of Subjects Experiencing Solicited Events with 95% Confidence Intervals by Symptom and Treatment Group, Asymptomatic Giardiasis Group

	Auranofin, 6 mg (N=X)			Placebo (N=X)		
Symptom	n	%	95% CI	n	%	95% CI
Stomatitis						
Conjunctivitis						
Glossitis						
Hematuria						
Rash						
N = Number of subjects in the Safety Analysis Population who received the specified dose. Severity is the maximum severity reported.						

Table will be repeated for the symptomatic study population but will exclude loose stools or diarrhea.

14.3.1.2 Unsolicited Adverse Events

Table 37: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, Relationship, Asymptomatic Amebiasis Group, Auranofin, 6 mg (n=x)

MedDRA System Organ Class	MedDRA Preferred Term	Any Incidence		Severity [1]						Relationship to Treatment [2]			
				Mild		Moderate		Severe		Not Related		Related	
		n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	Any PT	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
[SOC 1]	Any PT												
	[PT 1]												
	[PT 2]												
[SOC 2]	Any PT												
	[PT 1]												
	[PT 2]												

Note: N = Number of subjects in the Safety Analysis Population.
[1] For severity, a subject is counted once per preferred term and is summarized according to their highest severity.
[2] For relationship, a subject is only counted once per preferred term and is summarized according to their closest relationship.

Table will be repeated for the symptomatic study population.

Table 38: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, Relationship, Asymptomatic Amebiasis Group, Placebo (n=x)

MedDRA System Organ Class	MedDRA Preferred Term	Any Incidence		Severity [1]						Relationship to Treatment [2]			
				Mild		Moderate		Severe		Not Related		Related	
		n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	Any PT	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
[SOC 1]	Any PT												
	[PT 1]												
	[PT 2]												
[SOC 2]	Any PT												
	[PT 1]												
	[PT 2]												

Note: N = Number of subjects in the Safety Analysis Population.
[1] For severity, a subject is counted once per preferred term and is summarized according to their highest severity.
[2] For relationship, a subject is only counted once per preferred term and is summarized according to their closest relationship.

Table will be repeated for the symptomatic study population.

Table 39: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, Relationship, Asymptomatic Giardiasis Group, Auranofin, 6 mg (n=x)

MedDRA System Organ Class	MedDRA Preferred Term	Any Incidence		Severity [1]						Relationship to Treatment [2]			
				Mild		Moderate		Severe		Not Related		Related	
		n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	Any PT	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
[SOC 1]	Any PT												
	[PT 1]												
	[PT 2]												
[SOC 2]	Any PT												
	[PT 1]												
	[PT 2]												

Note: N = Number of subjects in the Safety Analysis Population.
[1] For severity, a subject is counted once per preferred term and is summarized according to their highest severity.
[2] For relationship, a subject is only counted once per preferred term and is summarized according to their closest relationship.

Table will be repeated for the symptomatic study population.

Table 40: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, Relationship, Asymptomatic Giardiasis Group, Placebo (n=x)

MedDRA System Organ Class	MedDRA Preferred Term	Any Incidence		Severity [1]						Relationship to Treatment [2]			
				Mild		Moderate		Severe		Not Related		Related	
		n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	Any PT	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
[SOC 1]	Any PT												
	[PT 1]												
	[PT 2]												
[SOC 2]	Any PT												
	[PT 1]												
	[PT 2]												

Note: N = Number of subjects in the Safety Analysis Population.
[1] For severity, a subject is counted once per preferred term and is summarized according to their highest severity.
[2] For relationship, a subject is only counted once per preferred term and is summarized according to their closest relationship.

Table will be repeated for the symptomatic study population.

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Table 41: Listing of Serious Adverse Events

Listings will be sorted by study population, disease group, treatment group, subject ID

Adverse Event	Associated with Dose No.	No. of Days Post Associated Dose (Duration)	No. of Days Post Dose the Event Became Serious	Reason Reported as an SAE	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Subject ID: , Study Population: , Disease Group: , Treatment Group: , AE Number:												
Comments:												
Subject ID: , Study Population: , Disease Group: , Treatment Group: , AE Number:												
Comments:												

Table 42: Listing of Non-Serious, Unsolicited, Moderate or Severe Adverse Events, Asymptomatic Amebiasis Group

Table will be repeated for the symptomatic population.

Adverse Event	Associated with Dose No.	No. of Days Post Associated Dose (Duration)	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Subject ID: , Treatment Group: , AE Number:										
Comments:										
Subject ID: , Treatment Group: , AE Number:										
Comments:										

Table 43: Listing of Non-Serious, Unsolicited, Moderate or Severe Adverse Events, Asymptomatic Giardiasis Group

Table will be repeated for the symptomatic population.

Adverse Event	Associated with Dose No.	No. of Days Post Associated Dose (Duration)	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Subject ID: , Treatment Group: , AE Number:										
Comments:										
Subject ID: , Treatment Group: , AE Number:										
Comments:										

14.3.3 Narratives of Deaths, Other Serious and Significant Adverse Events

(not included in SAP, but this is a placeholder for the CSR)

[This section of the clinical study report will include narrative text of deaths, serious, and significant adverse events.]

14.3.4 Abnormal Laboratory Value Listings (by Subject)

Table 44: Listing of Abnormal Laboratory Results, Asymptomatic Amebiasis Group

Subject ID	Treatment Group	Sex	Age (years)	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	If Not Related, Alternate Etiology	Action Taken with Study Treatment	Subject Discontinued Due to Result?

Table 45: Listing of Abnormal Laboratory Results, Asymptomatic Giardiasis Group

Subject ID	Treatment Group	Sex	Age (years)	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	If Not Related, Alternate Etiology	Action Taken with Study Treatment	Subject Discontinued Due to Result?

Repeat for symptomatic study population.

14.3.5 Displays of Laboratory Results

Table 46: Laboratory Results by Parameter, Maximum Severity, Study Day, and Treatment Group, Asymptomatic Amebiasis Group - Any Laboratory Parameter

Any laboratory parameter	Treatment Group	N	None		Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Auranofin, 6 mg	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo																	
Day 7	Auranofin, 6 mg																	
	Placebo																	

Repeat for symptomatic study population.

Table 47: Laboratory Results by Parameter, Maximum Severity, Study Day, and Treatment Group, Asymptomatic Amebiasis Group - White Blood Cell Count

White Blood Cell Count	Treatment Group	N	None		Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Auranofin, 6 mg	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo																	
Day 7	Auranofin, 6 mg																	
	Placebo																	

Repeat for symptomatic study population.

Table 48: Laboratory Results by Parameter, Maximum Severity, Study Day, and Treatment Group, Asymptomatic Amebiasis Group - Hemoglobin

Hemoglobin	Treatment Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Auranofin, 6 mg	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo											
Day 7	Auranofin, 6 mg											
	Placebo											

Repeat for symptomatic study population.

Table 49: Laboratory Results by Parameter, Maximum Severity, Study Day, and Treatment Group, Asymptomatic Amebiasis Group - Hematocrit

Hematocrit	Treatment Group	N	None		Mild Grade 1		Moderate Grade 2		Severe Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Auranofin, 6 mg	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo											
Day 7	Auranofin, 6 mg											
	Placebo											

Repeat for symptomatic study population.

Table 50: Laboratory Results by Parameter, Maximum Severity, Study Day, and Treatment Group, Asymptomatic Amebiasis Group - Platelets

Platelets	Treatment Group	N	None		Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Auranofin, 6 mg	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo																	
Day 7	Auranofin, 6 mg																	
	Placebo																	

Repeat for symptomatic study population.

Table 51: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Study Day, and Treatment Group, Asymptomatic Amebiasis Group -White Blood Cell Count

White Blood Cell Count	Treatment Group	N	Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Auranofin, 6 mg	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo															
Day 7	Auranofin, 6 mg															
	Placebo															

Repeat for symptomatic study population.

Table 52: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Study Day, and Treatment Group, Asymptomatic Amebiasis Group - Hemoglobin

Hemoglobin	Treatment Group	N	Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%
Baseline	Auranofin, 6 mg	x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo									
Day 7	Auranofin, 6 mg									

Repeat for symptomatic study population.

Table 53: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Study Day, and Treatment Group, Asymptomatic Amebiasis Group - Hematocrit

Hematocrit	Treatment Group	N	Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%
Baseline	Auranofin, 6 mg	x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo									
Day 7	Auranofin, 6 mg									
	Placebo									

Repeat for symptomatic study population.

Table 54: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Study Day, and Treatment Group, Asymptomatic Amebiasis Group - Platelets

Platelets	Treatment Group	N	Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Auranofin, 6 mg	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo															
Day 7	Auranofin, 6 mg															
	Placebo															

Repeat for symptomatic study population

Table 55: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Study Day, and Treatment Group, Asymptomatic Giardiasis Group -White Blood Cell Count

White Blood Cell Count	Treatment Group	N	Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Auranofin, 6 mg	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo															
Day 7	Auranofin, 6 mg															
	Placebo															

Repeat for symptomatic study population.

Table 56: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Study Day, and Treatment Group, Asymptomatic Giardiasis Group - Hemoglobin

Hemoglobin	Treatment Group	N	Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%
Baseline	Auranofin, 6 mg	x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo									
Day 7	Auranofin, 6 mg									
	Placebo									

Repeat for symptomatic study population.

Table 57: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Study Day, and Treatment Group, Asymptomatic Giardiasis Group - Hematocrit

Hematocrit	Treatment Group	N	Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%
Baseline	Auranofin, 6 mg	x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo									
Day 7	Auranofin, 6 mg									
	Placebo									

Repeat for symptomatic study population.

Table 58: Abnormal Laboratory Results Related to Study Treatment by Parameter, Maximum Severity, Study Day, and Treatment Group, Asymptomatic Giardiasis Group - Platelets

Platelets	Treatment Group	N	Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Auranofin, 6 mg	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo															
Day 7	Auranofin, 6 mg															
	Placebo															

Repeat for symptomatic study population.

Table 59: Laboratory Summary Statistics by Parameter, Study Day, and Treatment Group, Asymptomatic Amebiasis Group - White Blood Cells

Time Point	Treatment Group	N	Mean	Standard Deviation	Median	Min, Max
Baseline	Auranofin, 6 mg	x	xx.xx	xx.xx	xx.x	xx.x, xx.x
	Placebo					
Day 7	Auranofin, 6 mg					
	Placebo					
Day 7, Change from Baseline	Auranofin, 6 mg					
	Placebo					
N = Number of subjects in the Safety population with non-missing values for the parameter of interest.						

Repeat for symptomatic study population.

Table 60: Laboratory Summary Statistics by Parameter, Study Day, and Treatment Group, Asymptomatic Amebiasis Group - Hemoglobin

Time Point	Treatment Group	N	Mean	Standard Deviation	Median	Min, Max
Baseline	Auranofin, 6 mg	x	xx.xx	xx.xx	xx.x	xx.x, xx.x
	Placebo					
Day 7	Auranofin, 6 mg					
	Placebo					
Day 7, Change from Baseline	Auranofin, 6 mg					
	Placebo					
N = Number of subjects in the Safety population with non-missing values for the parameter of interest.						

Repeat for symptomatic study population.

Table 61: Laboratory Summary Statistics by Parameter, Study Day, and Treatment Group, Asymptomatic Amebiasis Group -Hematocrit

Time Point	Treatment Group	N	Mean	Standard Deviation	Median	Min, Max
Baseline	Auranofin, 6 mg	x	xx.x	xx.x	x	xx, xx
	Placebo					
Day 7	Auranofin, 6 mg					
	Placebo					
Day 7, Change from Baseline	Auranofin, 6 mg					
	Placebo					
N = Number of subjects in the Safety population with non-missing values for the parameter of interest.						

Repeat for symptomatic study population.

Table 62: Laboratory Summary Statistics by Parameter, Study Day, and Treatment Group, Asymptomatic Amebiasis Group - Platelets

Time Point	Treatment Group	N	Mean	Standard Deviation	Median	Min, Max
Baseline	Auranofin, 6 mg	x	xx.xx	xx.xx	xx.x	xx.x, xx.x
	Placebo					
Day 7	Auranofin, 6 mg					
	Placebo					
Day 7, Change from Baseline	Auranofin, 6 mg					
	Placebo					
N = Number of subjects in the Safety population with non-missing values for the parameter of interest.						

Repeat for symptomatic study population.

Table 63: Laboratory Summary Statistics by Parameter, Study Day, and Treatment Group, Asymptomatic Giardiasis Group - White Blood Cells

Time Point	Treatment Group	N	Mean	Standard Deviation	Median	Min, Max
Baseline	Auranofin, 6 mg	x	xx.xx	xx.xx	xx.x	xx.x, xx.x
	Placebo					
Day 7	Auranofin, 6 mg					
	Placebo					
Day 7, Change from Baseline	Auranofin, 6 mg					
	Placebo					
N = Number of subjects in the Safety population with non-missing values for the parameter of interest.						

Repeat for symptomatic study population.

Table 64: Laboratory Summary Statistics by Parameter, Study Day, and Treatment Group, Asymptomatic Giardiasis Group - Hemoglobin

Time Point	Treatment Group	N	Mean	Standard Deviation	Median	Min, Max
Baseline	Auranofin, 6 mg	x	xx.xx	xx.xx	xx.x	xx.x, xx.x
	Placebo					
Day 7	Auranofin, 6 mg					
	Placebo					
Day 7, Change from Baseline	Auranofin, 6 mg					
	Placebo					
N = Number of subjects in the Safety population with non-missing values for the parameter of interest.						

Repeat for symptomatic study population.

Table 65: Laboratory Summary Statistics by Parameter, Study Day, and Treatment Group, Asymptomatic Giardiasis Group - Hematocrit

Time Point	Treatment Group	N	Mean	Standard Deviation	Median	Min, Max
Baseline	Auranofin, 6 mg	x	xx.x	xx.x	x	xx, xx
	Placebo					
Day 7	Auranofin, 6 mg					
	Placebo					
Day 7, Change from Baseline	Auranofin, 6 mg					
	Placebo					
N = Number of subjects in the Safety population with non-missing values for the parameter of interest.						

Repeat for symptomatic study population.

Table 66: Laboratory Summary Statistics by Parameter, Study Day, and Treatment Group, Asymptomatic Giardiasis Group - Platelets

Time Point	Treatment Group	N	Mean	Standard Deviation	Median	Min, Max
Baseline	Auranofin, 6 mg	x	xx.xx	xx.xx	xx.x	xx.x, xx.x
	Placebo					
Day 7	Auranofin, 6 mg					
	Placebo					
Day 7, Change from Baseline	Auranofin, 6 mg					
	Placebo					
N = Number of subjects in the Safety population with non-missing values for the parameter of interest.						

Repeat for symptomatic study population.

14.3.6 Displays of Vital Signs

Table 67: Vital Signs by Assessment, Maximum Severity, Study Day, and Treatment Group, Amebiasis Group - Any Assessment

This table series will be repeated for the symptomatic study population.

Time Point	Treatment Group	N	None		Mild		Moderate		Severe		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Auranofin, 6 mg	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo											
Day 1	Auranofin, 6 mg											
	Placebo											
Day 2	Auranofin, 6 mg											
	Placebo											
Day 3	Auranofin, 6 mg											
	Placebo											
Day 4	Auranofin, 6 mg											
	Placebo											
Day 5	Auranofin, 6 mg											
	Placebo											
Day 6	Auranofin, 6 mg											
	Placebo											
Day 7	Auranofin, 6 mg											
	Placebo											
Day 14	Auranofin, 6 mg											
	Placebo											
Day 28	Auranofin, 6 mg											
	Placebo											
Max Severity Post Baseline	Auranofin, 6 mg											
	Placebo											

Note: The “Max Post Baseline” rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N=Number of subjects in the Safety population with non-missing values.

Table 68: Vital Signs by Assessment, Maximum Severity, Study Day, and Treatment Group, Amebiasis Group - Fever

Time Point	Treatment Group	N	None		Mild		Moderate		Severe		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Auranofin, 6 mg	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo											
Day 1	Auranofin, 6 mg											
	Placebo											
Day 2	Auranofin, 6 mg											
	Placebo											
Day 3	Auranofin, 6 mg											
	Placebo											
Day 4	Auranofin, 6 mg											
	Placebo											
Day 5	Auranofin, 6 mg											
	Placebo											
Day 6	Auranofin, 6 mg											
	Placebo											
Day 7	Auranofin, 6 mg											
	Placebo											
Day 14	Auranofin, 6 mg											
	Placebo											
Day 28	Auranofin, 6 mg											
	Placebo											
Max Severity Post Baseline	Auranofin, 6 mg											
	Placebo											

Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post ncluding unscheduled assessments. N=Number of subjects in the Safety population with non-missing values.

Table 69: Vital Signs by Assessment, Maximum Severity, Study Day, and Treatment Group, Amebiasis Group - Systolic Blood Pressure (Hypertension/Hypotension)

Time Point	Treatment Group	N	None		Mild (Low)		Mild (High)		Moderate (Low)		Moderate (High)		Severe (Low)		Severe (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Auranofin, 6 mg	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo																	
Day 1	Auranofin, 6 mg																	
	Placebo																	
Day 2	Auranofin, 6 mg																	
	Placebo																	
Day 3	Auranofin, 6 mg																	
	Placebo																	
Day 4	Auranofin, 6 mg																	
	Placebo																	
Day 5	Auranofin, 6 mg																	
	Placebo																	
Day 6	Auranofin, 6 mg																	
	Placebo																	
Day 7	Auranofin, 6 mg																	
	Placebo																	
Day 14	Auranofin, 6 mg																	
	Placebo																	
Day 28	Auranofin, 6 mg																	
	Placebo																	
Max Severity Post Baseline	Auranofin, 6 mg																	
	Placebo																	

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N=Number of subjects in the Safety population with non-missing values

Table 70: Vital Signs by Assessment, Maximum Severity, Study Day, and Treatment Group, Amebiasis Group - Diastolic Blood Pressure - Hypertension

Time Point	Treatment Group	N	None		Mild		Moderate		Severe		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Auranofin, 6 mg	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo											
Day 1	Auranofin, 6 mg											
	Placebo											
Day 2	Auranofin, 6 mg											
	Placebo											
Day 3	Auranofin, 6 mg											
	Placebo											
Day 4	Auranofin, 6 mg											
	Placebo											
Day 5	Auranofin, 6 mg											
	Placebo											
Day 6	Auranofin, 6 mg											
	Placebo											
Day 7	Auranofin, 6 mg											
	Placebo											
Day 14	Auranofin, 6 mg											
	Placebo											
Day 28	Auranofin, 6 mg											
	Placebo											
Max Severity Post Baseline	Auranofin, 6 mg											
	Placebo											

Note: The “Max Post Baseline” rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N=Number of subjects in the Safety population with non-missing values.

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Table 71: Vital Signs by Assessment, Maximum Severity, Study Day, and Treatment Group, Amebiasis Group -Bradycardia

Time Point	Treatment Group	N	None		Mild		Moderate		Severe		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Auranofin, 6 mg	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo											
Day 1	Auranofin, 6 mg											
	Placebo											
Day 2	Auranofin, 6 mg											
	Placebo											
Day 3	Auranofin, 6 mg											
	Placebo											
Day 4	Auranofin, 6 mg											
	Placebo											
Day 5	Auranofin, 6 mg											
	Placebo											
Day 6	Auranofin, 6 mg											
	Placebo											
Day 7	Auranofin, 6 mg											
	Placebo											
Day 14	Auranofin, 6 mg											
	Placebo											
Day 28	Auranofin, 6 mg											
	Placebo											
Max Severity Post Baseline	Auranofin, 6 mg											
	Placebo											

Note: The “Max Post Baseline” rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N=Number of subjects in the Safety population with non-missing values.

Table 72: Vital Signs by Assessment, Maximum Severity, Study Day, and Treatment Group, Amebiasis Group - Tachycardia

Time Point	Treatment Group	N	None		Mild		Moderate		Severe		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Auranofin, 6 mg	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo											
Day 1	Auranofin, 6 mg											
	Placebo											
Day 2	Auranofin, 6 mg											
	Placebo											
Day 3	Auranofin, 6 mg											
	Placebo											
Day 4	Auranofin, 6 mg											
	Placebo											
Day 5	Auranofin, 6 mg											
	Placebo											
Day 6	Auranofin, 6 mg											
	Placebo											
Day 7	Auranofin, 6 mg											
	Placebo											
Day 14	Auranofin, 6 mg											
	Placebo											
Day 28	Auranofin, 6 mg											
	Placebo											
Max Severity Post Baseline	Auranofin, 6 mg											
	Placebo											

Note: The “Max Post Baseline” rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N=Number of subjects in the Safety population with non-missing values.

Table 73: Vital Signs by Assessment, Maximum Severity, Study Day, and Treatment Group, Giardiasis Group - Any Assessment

This table series will be repeated for the symptomatic study population.

Time Point	Treatment Group	N	None		Mild		Moderate		Severe		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Auranofin, 6 mg	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo											
Day 1	Auranofin, 6 mg											
	Placebo											
Day 2	Auranofin, 6 mg											
	Placebo											
Day 3	Auranofin, 6 mg											
	Placebo											
Day 4	Auranofin, 6 mg											
	Placebo											
Day 5	Auranofin, 6 mg											
	Placebo											
Day 6	Auranofin, 6 mg											
	Placebo											
Day 7	Auranofin, 6 mg											
	Placebo											
Day 14	Auranofin, 6 mg											
	Placebo											
Day 28	Auranofin, 6 mg											
	Placebo											
Max Severity Post Baseline	Auranofin, 6 mg											
	Placebo											

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N=Number of subjects in the Safety population with non-missing values.

Table 74: Vital Signs by Assessment, Maximum Severity, Study Day, and Treatment Group, Giardiasis Group - Fever

Time Point	Treatment Group	N	None		Mild		Moderate		Severe		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Auranofin, 6 mg	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo											
Day 1	Auranofin, 6 mg											
	Placebo											
Day 2	Auranofin, 6 mg											
	Placebo											
Day 3	Auranofin, 6 mg											
	Placebo											
Day 4	Auranofin, 6 mg											
	Placebo											
Day 5	Auranofin, 6 mg											
	Placebo											
Day 6	Auranofin, 6 mg											
	Placebo											
Day 7	Auranofin, 6 mg											
	Placebo											
Day 14	Auranofin, 6 mg											
	Placebo											
Day 28	Auranofin, 6 mg											
	Placebo											
Max Severity Post Baseline	Auranofin, 6 mg											
	Placebo											

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N=Number of subjects in the Safety population with non-missing values.

Table 75: Vital Signs by Assessment, Maximum Severity, Study Day, and Treatment Group, Giardiasis Group - Systolic Blood Pressure - (Hypertension/Hypotension)

Time Point	Treatment Group	N	None		Mild (Low)		Mild (High)		Moderate (Low)		Moderate (High)		Severe (Low)		Severe (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Auranofin, 6 mg	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo																	
Day 1	Auranofin, 6 mg																	
	Placebo																	
Day 2	Auranofin, 6 mg																	
	Placebo																	
Day 3	Auranofin, 6 mg																	
	Placebo																	
Day 4	Auranofin, 6 mg																	
	Placebo																	
Day 5	Auranofin, 6 mg																	
	Placebo																	
Day 6	Auranofin, 6 mg																	
	Placebo																	
Day 7	Auranofin, 6 mg																	
	Placebo																	
Day 14	Auranofin, 6 mg																	
	Placebo																	
Day 28	Auranofin, 6 mg																	
	Placebo																	
Max Severity Post Baseline	Auranofin, 6 mg																	
	Placebo																	

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time at post baseline, including unscheduled assessments. N=Number of subjects in the Safety population with non-missing values.

Table 76: Vital Signs by Assessment, Maximum Severity, Study Day, and Treatment Group, Giardiasis Group - Diastolic Blood Pressure - Hypertension

Time Point	Treatment Group	N	None		Mild		Moderate		Severe		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Auranofin, 6 mg	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo											
Day 1	Auranofin, 6 mg											
	Placebo											
Day 2	Auranofin, 6 mg											
	Placebo											
Day 3	Auranofin, 6 mg											
	Placebo											
Day 4	Auranofin, 6 mg											
	Placebo											
Day 5	Auranofin, 6 mg											
	Placebo											
Day 6	Auranofin, 6 mg											
	Placebo											
Day 7	Auranofin, 6 mg											
	Placebo											
Day 14	Auranofin, 6 mg											
	Placebo											
Day 28	Auranofin, 6 mg											
	Placebo											
Max Severity Post Baseline	Auranofin, 6 mg											
	Placebo											

Note: The “Max Post Baseline” rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N=Number of subjects in the Safety population with non-missing values.

Table 77: Vital Signs by Assessment, Maximum Severity, Study Day, and Treatment Group, Giardiasis Group - Bradycardia

Time Point	Treatment Group	N	None		Mild		Moderate		Severe		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Auranofin, 6 mg	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo											
Day 1	Auranofin, 6 mg											
	Placebo											
Day 2	Auranofin, 6 mg											
	Placebo											
Day 3	Auranofin, 6 mg											
	Placebo											
Day 4	Auranofin, 6 mg											
	Placebo											
Day 5	Auranofin, 6 mg											
	Placebo											
Day 6	Auranofin, 6 mg											
	Placebo											
Day 7	Auranofin, 6 mg											
	Placebo											
Day 14	Auranofin, 6 mg											
	Placebo											
Day 28	Auranofin, 6 mg											
	Placebo											
Max Severity Post Baseline	Auranofin, 6 mg											
	Placebo											

Note: The “Max Post Baseline” rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N=Number of subjects in the Safety population with non-missing values.

Table 78: Vital Signs by Assessment, Maximum Severity, Study Day, and Treatment Group, Giardiasis Group - Tachycardia

Time Point	Treatment Group	N	None		Mild		Moderate		Severe		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Auranofin, 6 mg	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo											
Day 1	Auranofin, 6 mg											
	Placebo											
Day 2	Auranofin, 6 mg											
	Placebo											
Day 3	Auranofin, 6 mg											
	Placebo											
Day 4	Auranofin, 6 mg											
	Placebo											
Day 5	Auranofin, 6 mg											
	Placebo											
Day 6	Auranofin, 6 mg											
	Placebo											
Day 7	Auranofin, 6 mg											
	Placebo											
Day 14	Auranofin, 6 mg											
	Placebo											
Day 28	Auranofin, 6 mg											
	Placebo											
Max Severity Post Baseline	Auranofin, 6 mg											
	Placebo											

Note: The “Max Post Baseline” rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N=Number of subjects in the Safety population with non-missing values.

14.4 Summary of Concomitant Medications

Table 79: Number and Percentage of Subjects with Prior and Concurrent Medications by WHO Drug Classification and Treatment Group, Asymptomatic Amebiasis Group

This table will be repeated for the symptomatic population.

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	Auranofin, 6 mg (N=X)		Placebo (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Any Level 1 Codes	Any Level 2 Codes	x	x.x	x	x.x	x	x.x
[ATC Level 1 - 1]	Any [ATC 1 – 1]						
	[ATC 2 - 1]						
	[ATC 2 - 2]						
	[ATC 2 - 3]						
[ATC Level 1 – 2]	[ATC 2 - 1]						
	[ATC 2 - 2]						
	[ATC 2 - 3]						
N= Number of subjects in the Safety population with non-missing values							

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Table 80: Number and Percentage of Subjects with Prior and Concurrent Medications by WHO Drug Classification and Treatment Group, Asymptomatic Giardiasis Group

This table will be repeated for the symptomatic population.

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	Auranofin, 6 mg (N=X)		Placebo (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Any Level 1 Codes	Any Level 2 Codes	x	x.x	x	x.x	x	x.x
[ATC Level 1 - 1]	Any [ATC 1 – 1]						
	[ATC 2 - 1]						
	[ATC 2 - 2]						
	[ATC 2 - 3]						
[ATC Level 1 – 2]	[ATC 2 - 1]						
	[ATC 2 - 2]						
	[ATC 2 - 3]						
N= Number of subjects in the Safety population with non-missing values.							

APPENDIX 2. FIGURE MOCK-UPS

LIST OF FIGURES

9.1 Overall Study Design and Plan Description

Figure 1: Schematic of Study Design, Part 1

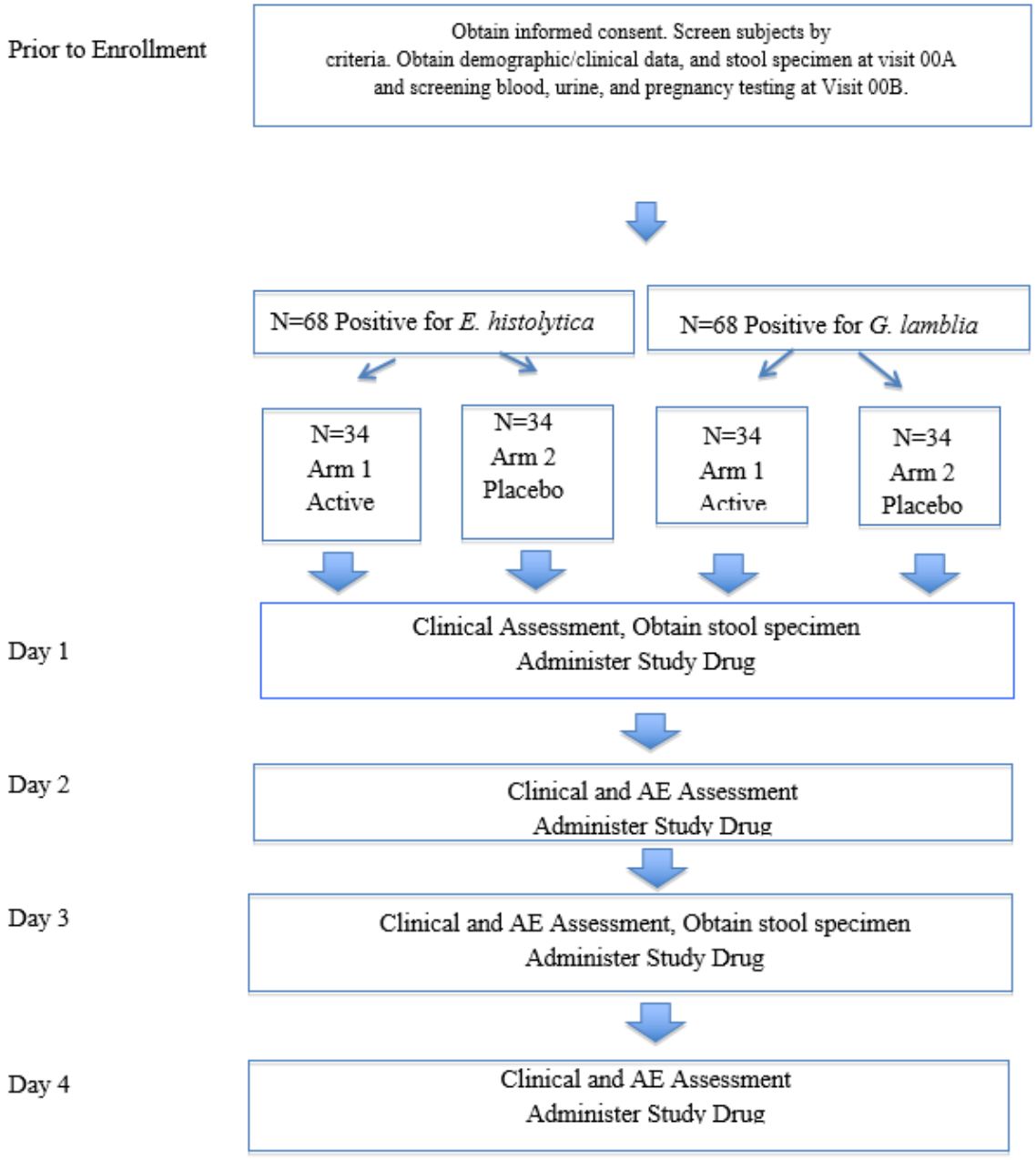
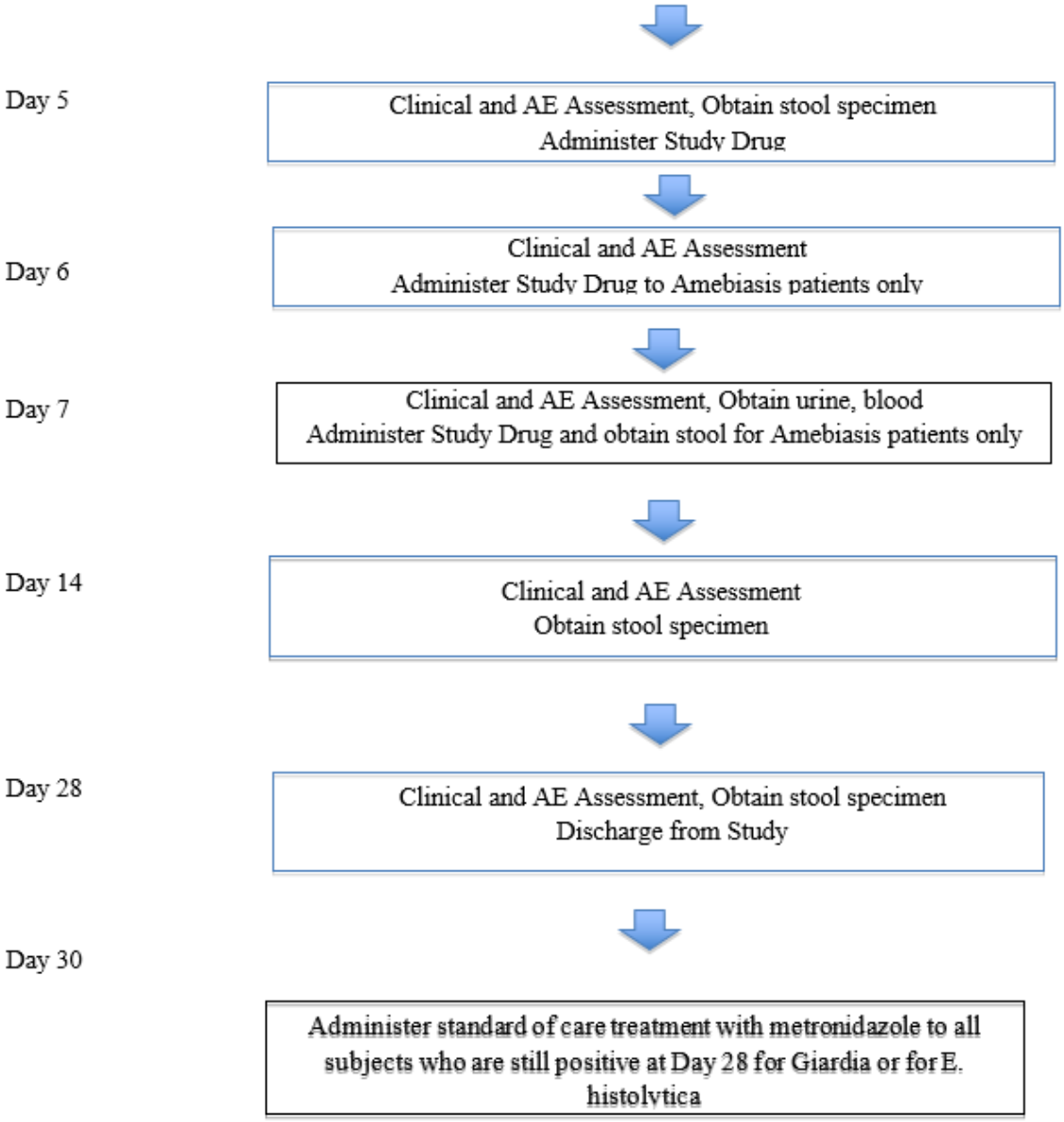
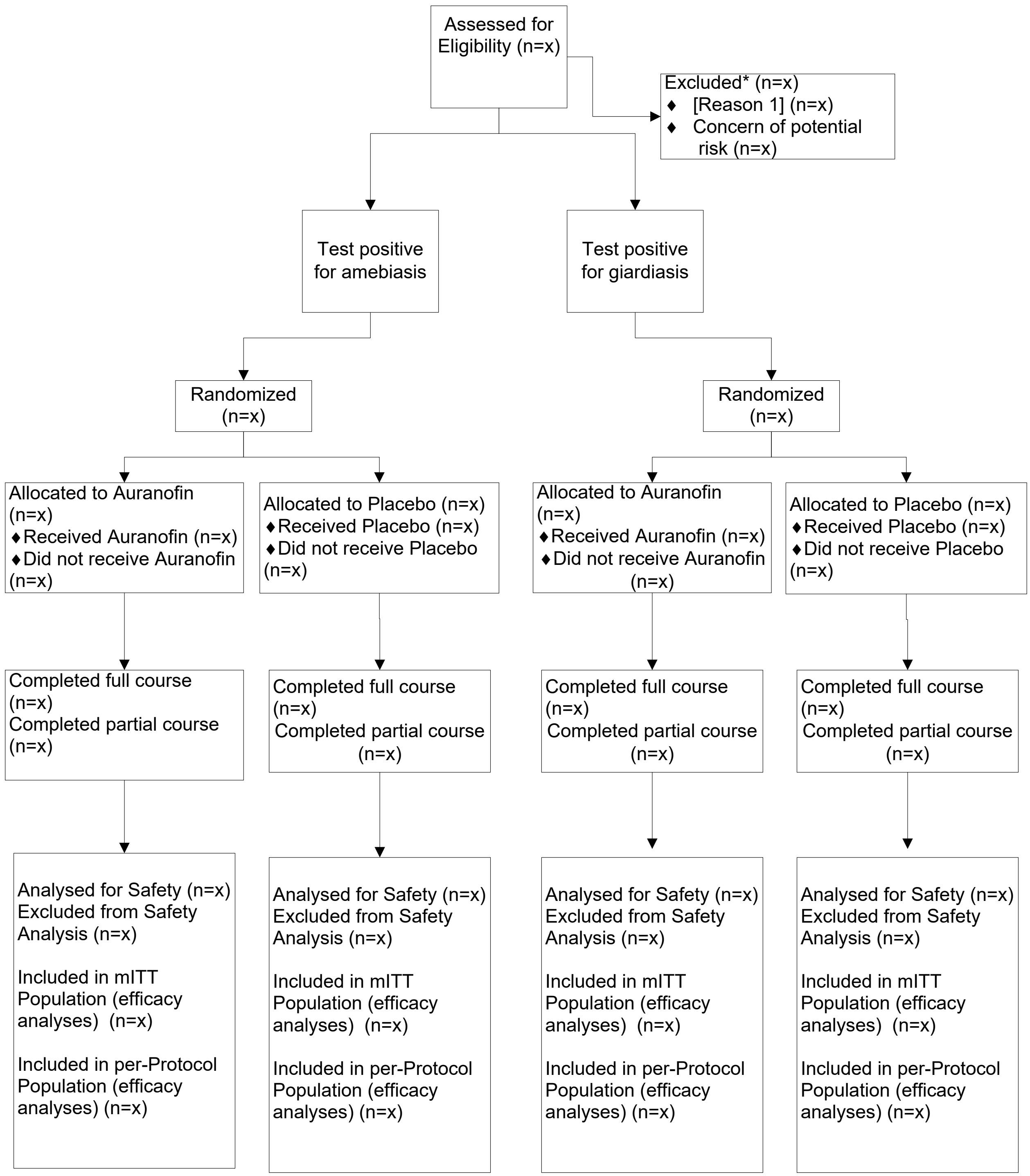


Figure 2: Schematic of Study Design, Part 2



10.1 Disposition of Subjects

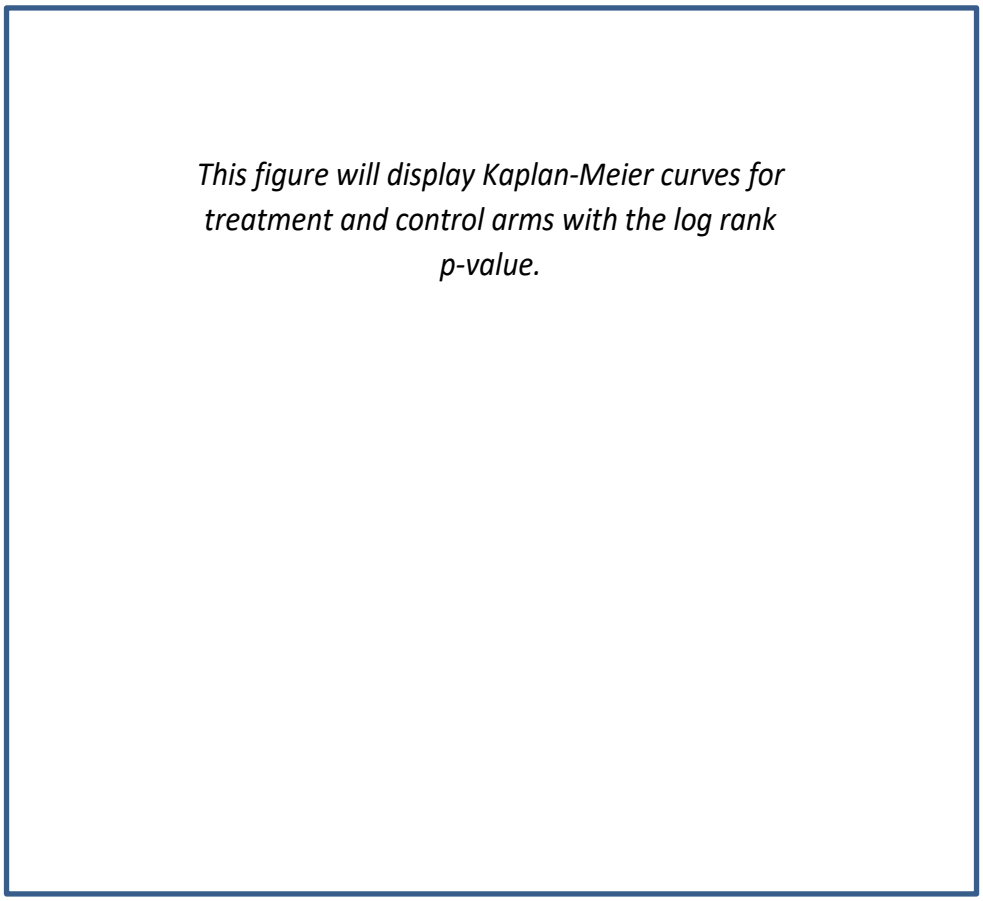
Figure 3: CONSORT Flow Diagram



14.2.2 Efficacy/Immunogenicity Response Figures by Measure, Treatment/Vaccination, and Time Point

Figure 4: Kaplan-Meier Curves of Time to Diarrhea Resolution, Symptomatic Amebiasis Group

Figure will be repeated for the symptomatic giardiasis group.



14.3.1.1 Solicited Adverse Events

Figure 5: Maximum Severity of Solicited Symptoms per Subject by Day Post Treatment And Treatment Group, Asymptomatic Amebiasis Group (N=68)

Figure will be repeated for the asymptomatic giardiasis, symptomatic amebiasis, and symptomatic giardiasis groups.

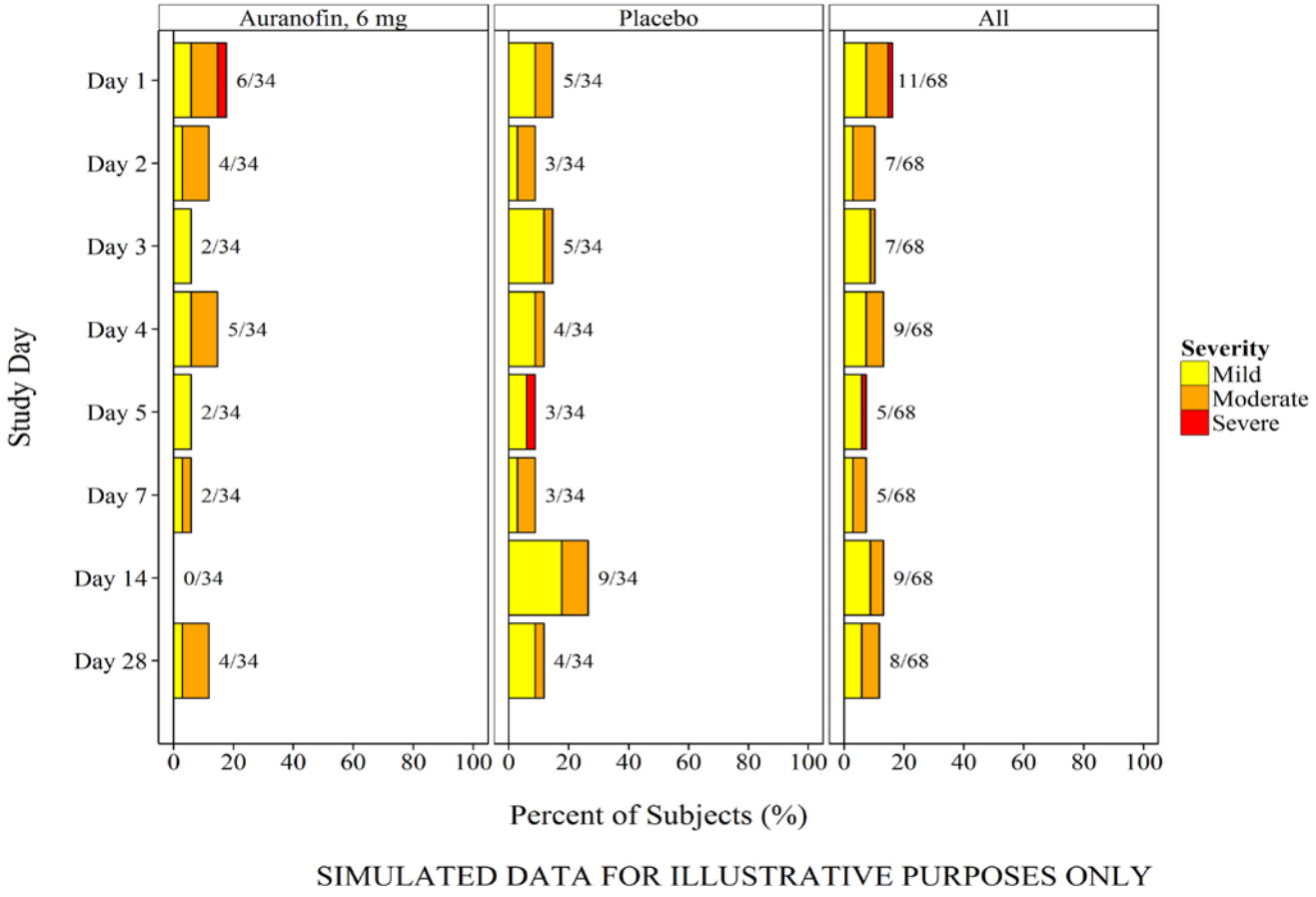
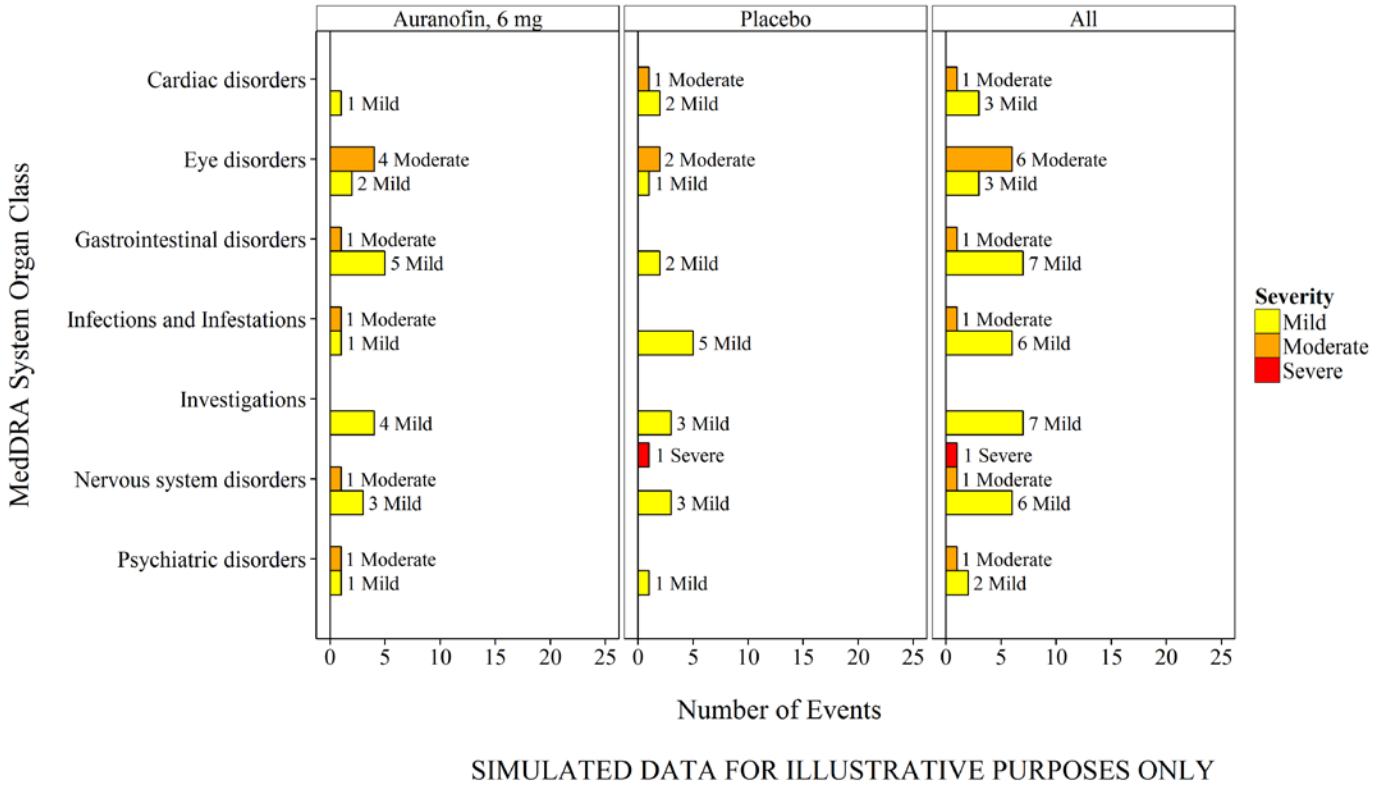


Figure 6: Frequency of Adverse Events by MedDRA System Organ Class and Severity Asymptomatic Amebiasis Group (N=68)

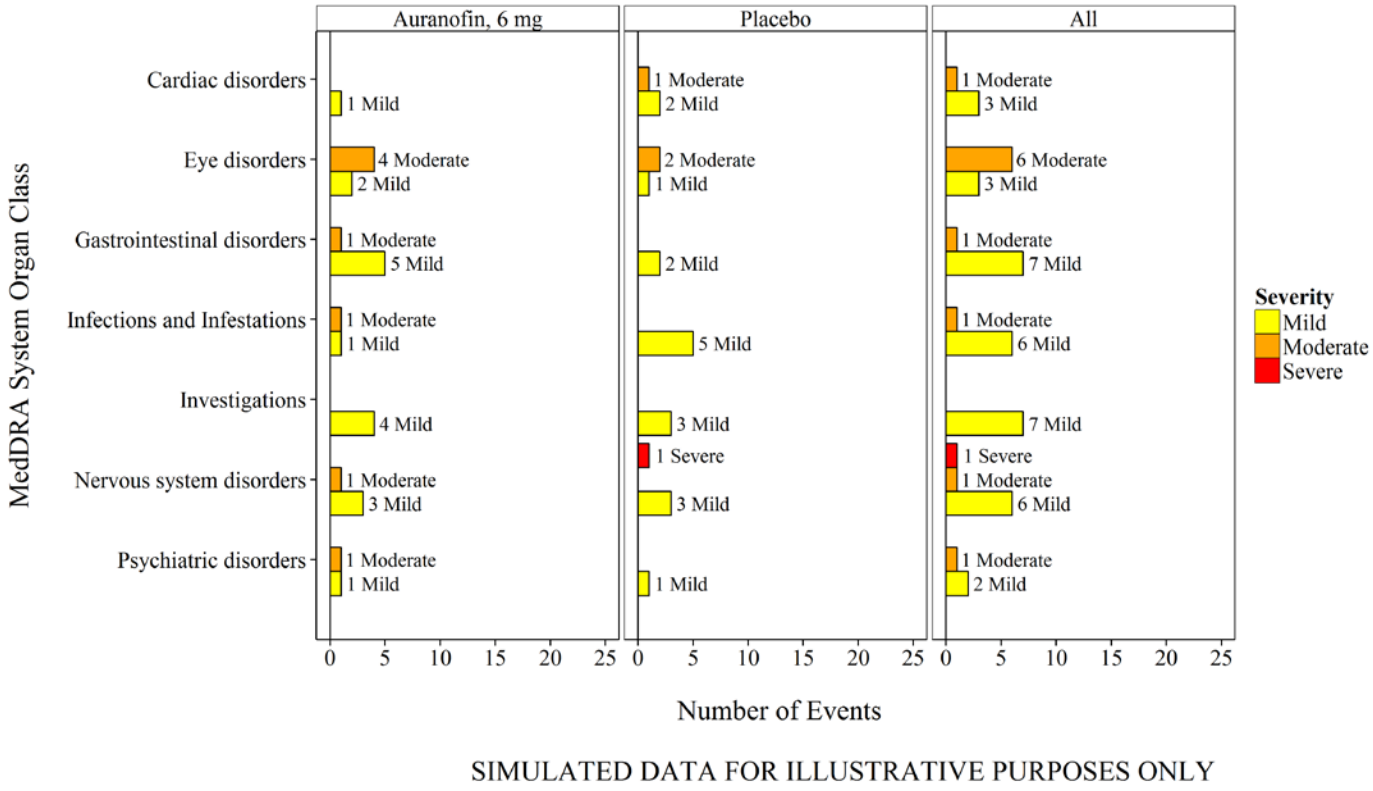
Figure will be repeated for the symptomatic amebiasis group.



14.3.1.2 Unsolicited Adverse Events

Figure 7: Frequency of Adverse Events by MedDRA System Organ Class and Severity Asymptomatic Giardiasis Group (N=68)

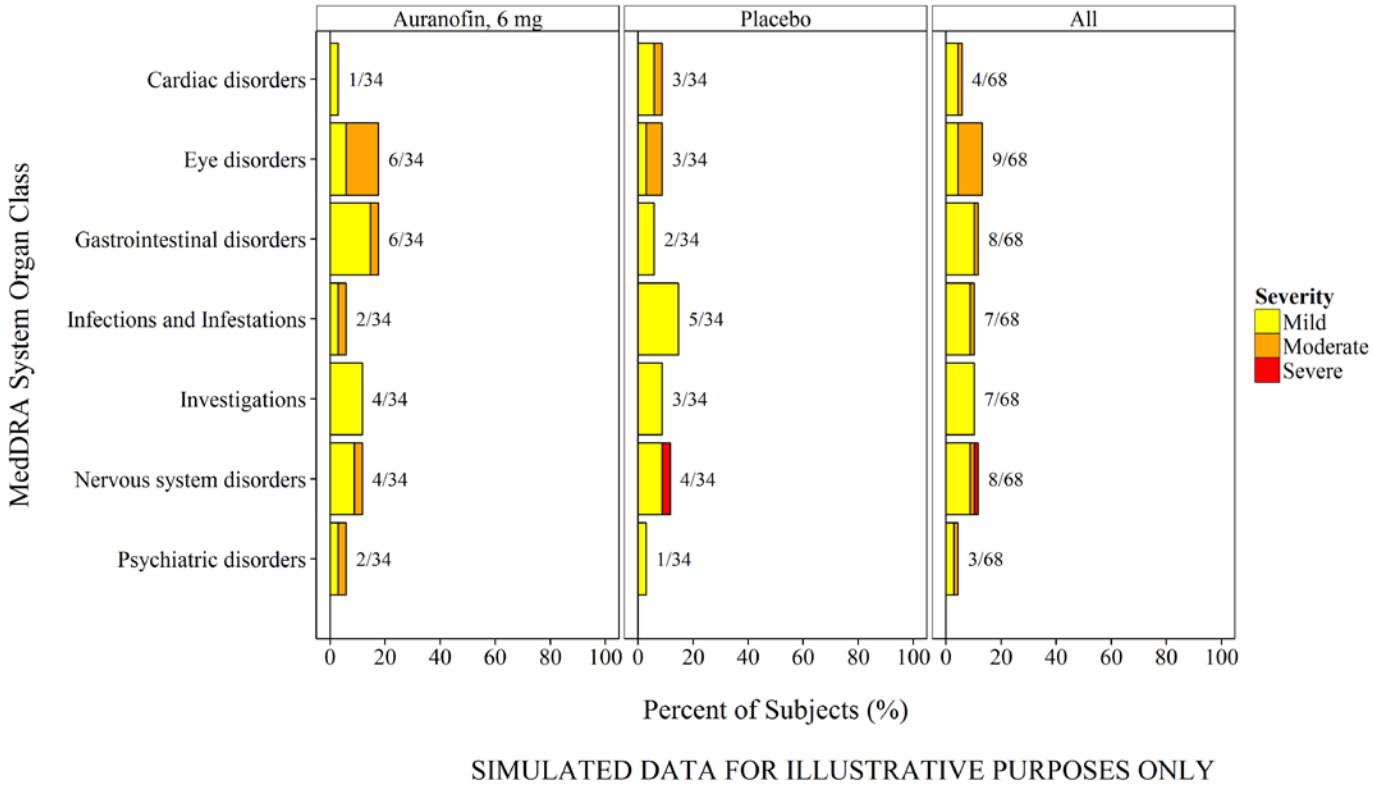
Figure will be repeated for the symptomatic giardiasis group.



SIMULATED DATA FOR ILLUSTRATIVE PURPOSES ONLY

Figure 8: Incidence of Adverse Events by MedDRA System Organ Class and Severity, Asymptomatic Amebiasis Group (N=68)

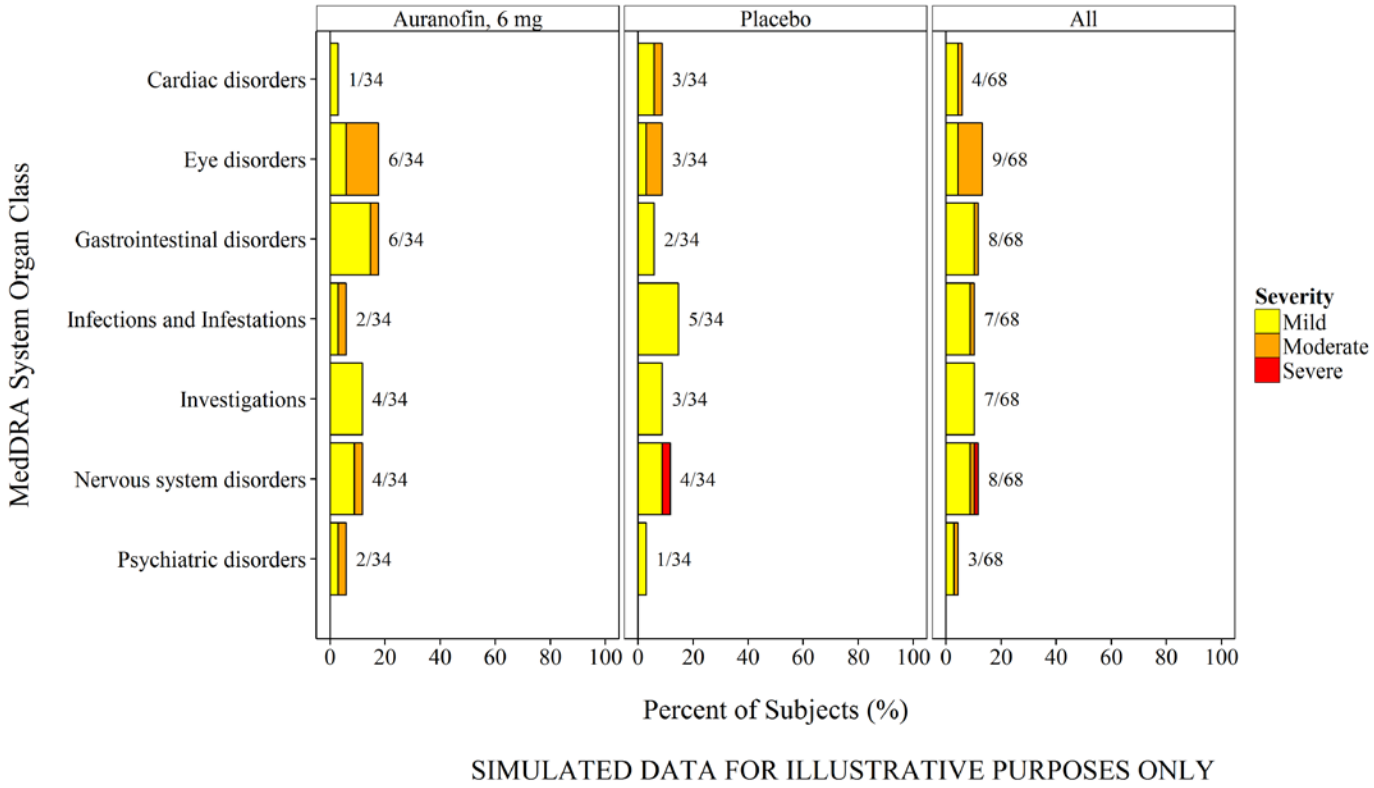
Figure will be repeated for the symptomatic amebiasis group.



SIMULATED DATA FOR ILLUSTRATIVE PURPOSES ONLY

Figure 9: Incidence of Adverse Events by MedDRA System Organ Class and Severity, Asymptomatic Giardiasis Group (N=68)

Figure will be repeated for the symptomatic giardiasis group.



SIMULATED DATA FOR ILLUSTRATIVE PURPOSES ONLY

Figure 10: Frequency of Unsolicited Adverse Events by Severity Asymptomatic Amebiasis Group (N=68)

Figure will be repeated for the symptomatic amebiasis group.

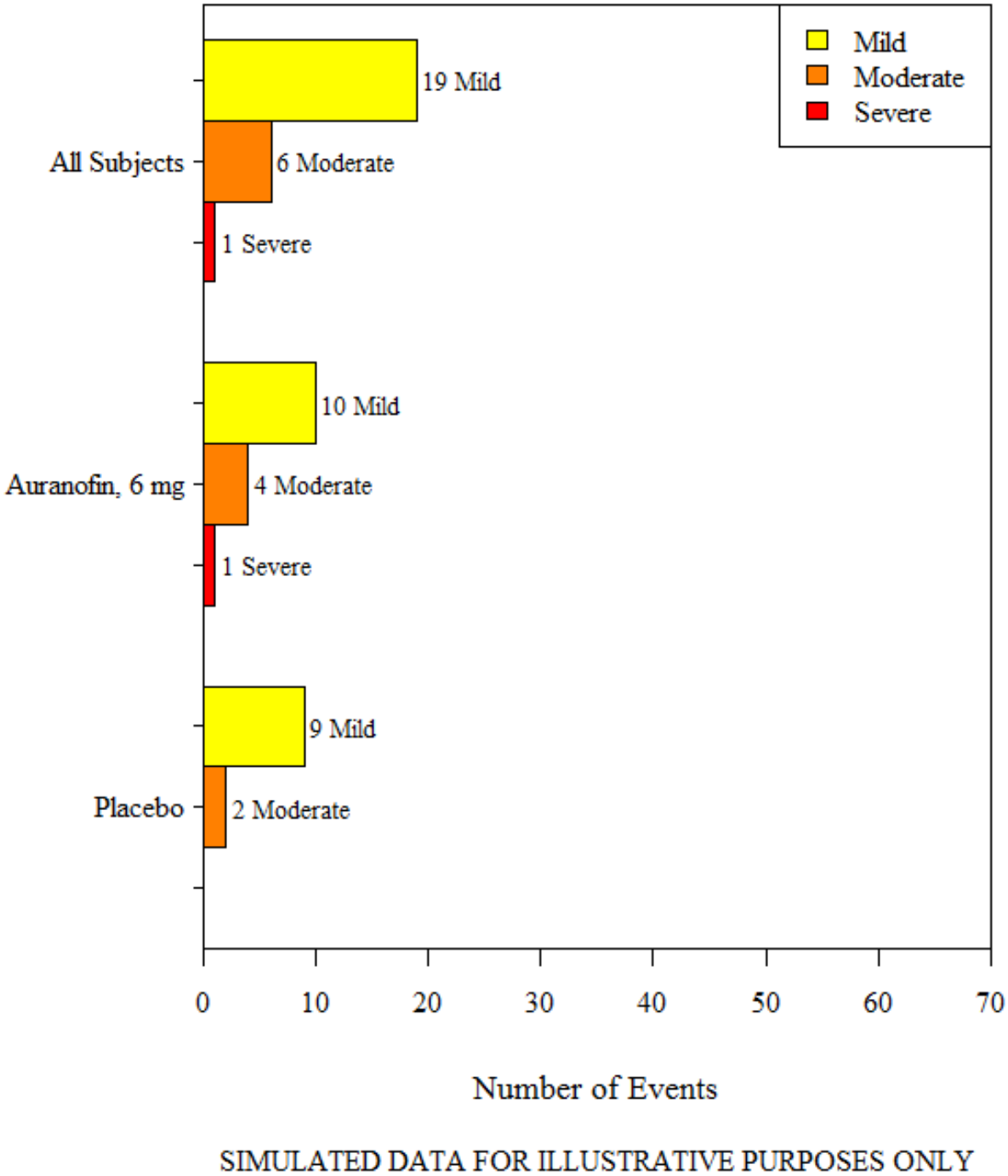


Figure 11: Frequency of Unsolicited Adverse Events by Severity Asymptomatic Giardiasis Group (N=68)

Figure will be repeated for the symptomatic giardiasis group

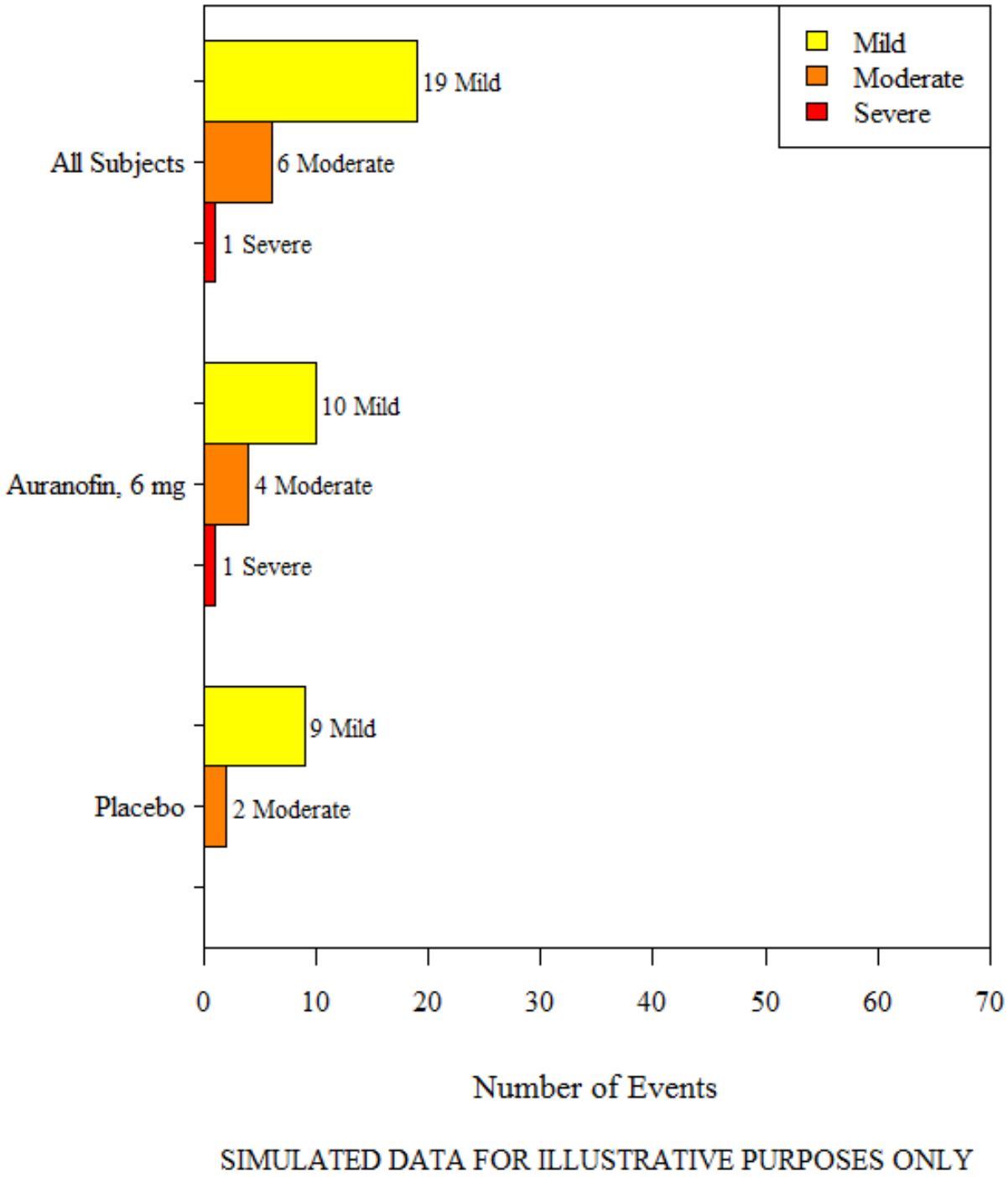


Figure 12: Incidence of Unsolicited Adverse Events by Asymptomatic Amebiasis Group (N=68)

Figure will be repeated for the symptomatic amebiasis group.

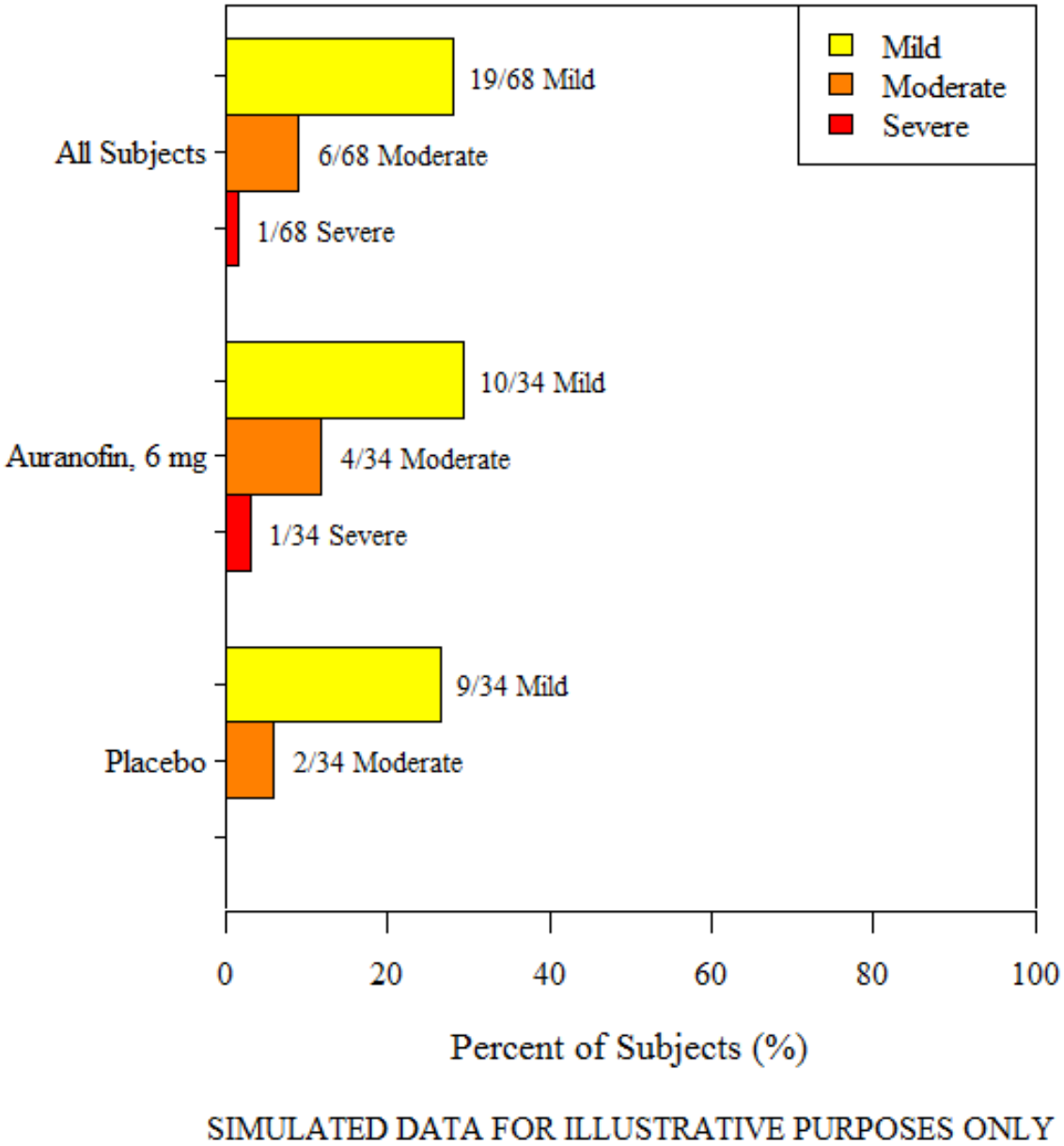


Figure 13: Incidence of Unsolicited Adverse Events by Severity Asymptomatic Giardiasis Group (N=68)

Figure will be repeated for the symptomatic giardiasis group.

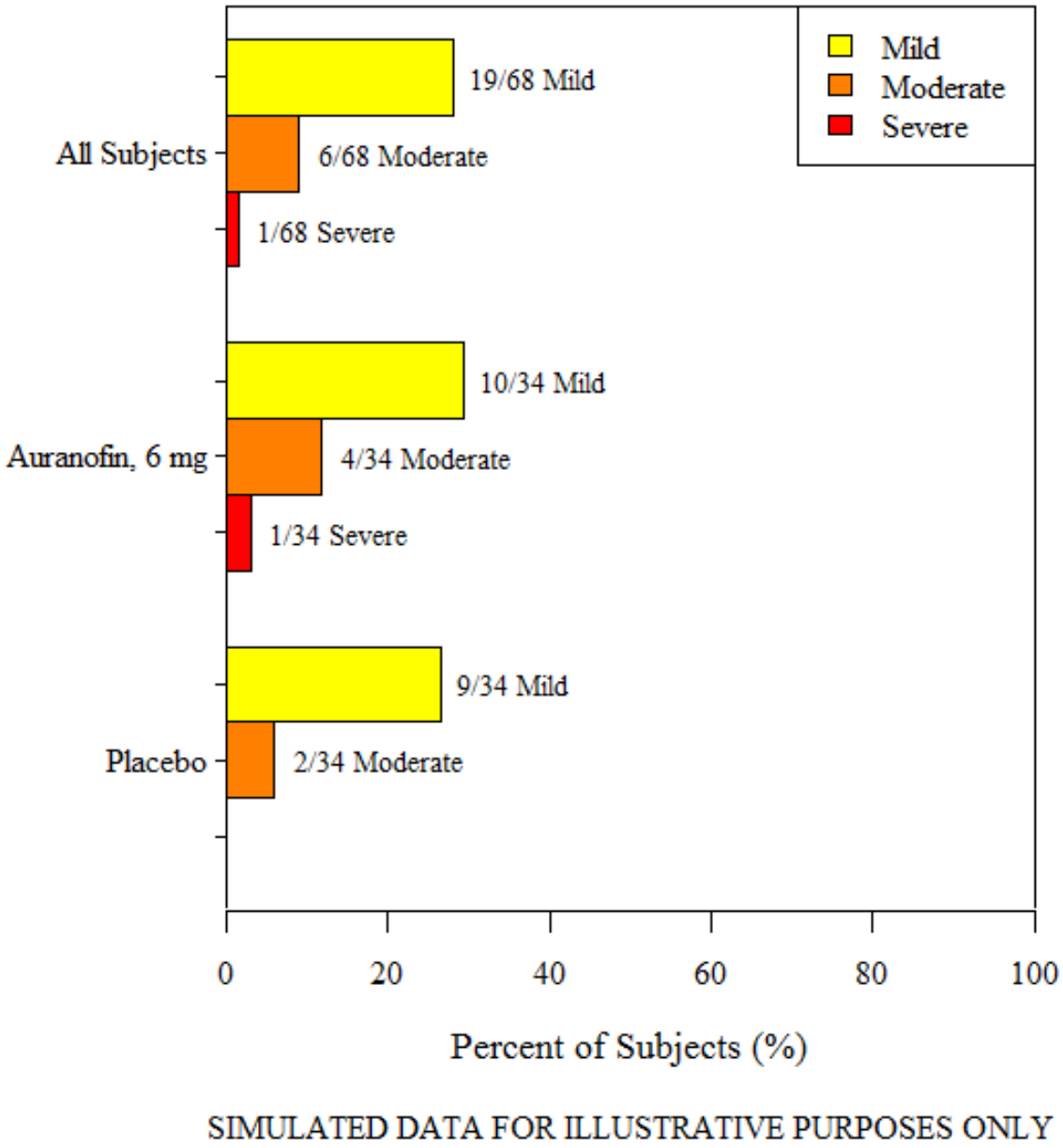
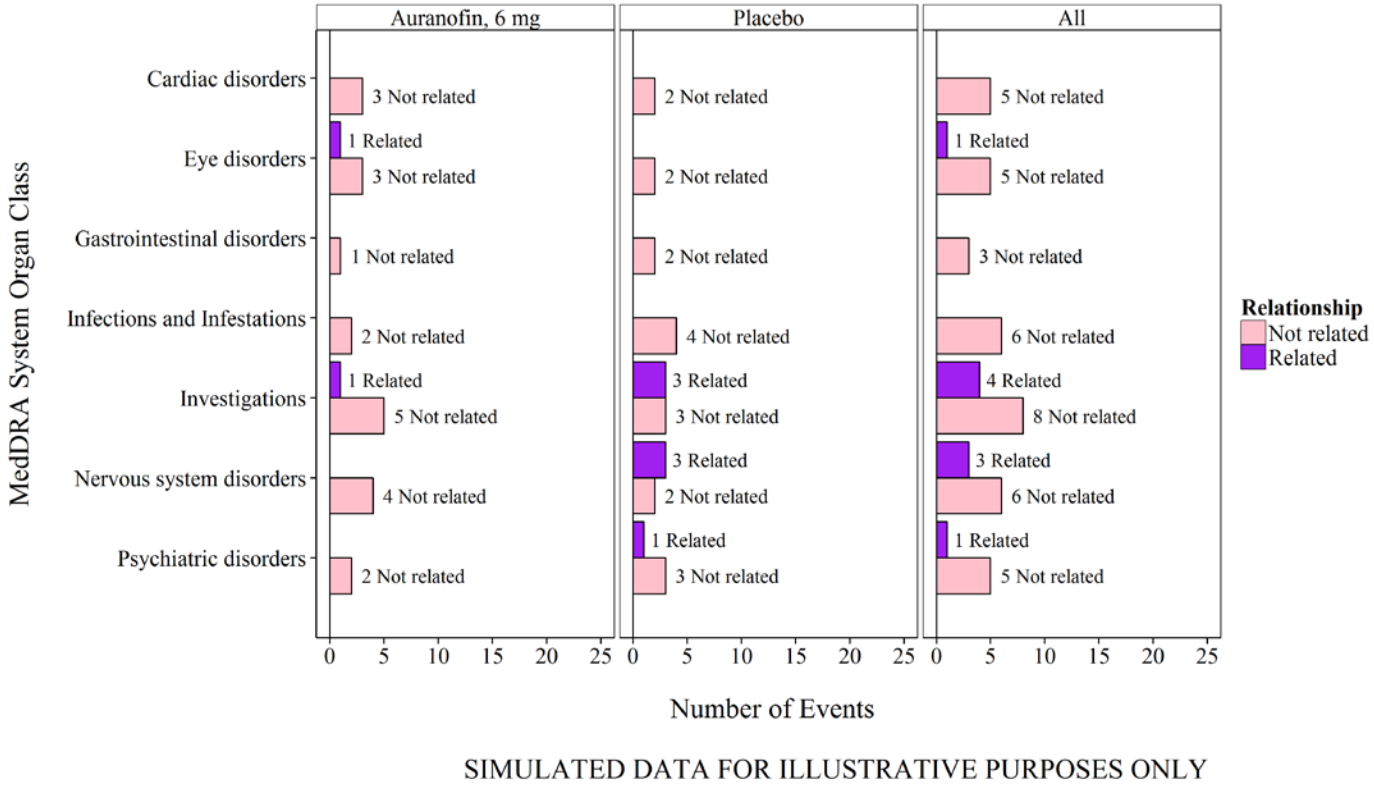


Figure 14: Frequency of Unsolicited Adverse Events by MedDRA System Organ Class and Relationship to Treatment - Asymptomatic Amebiasis Group (N=68)

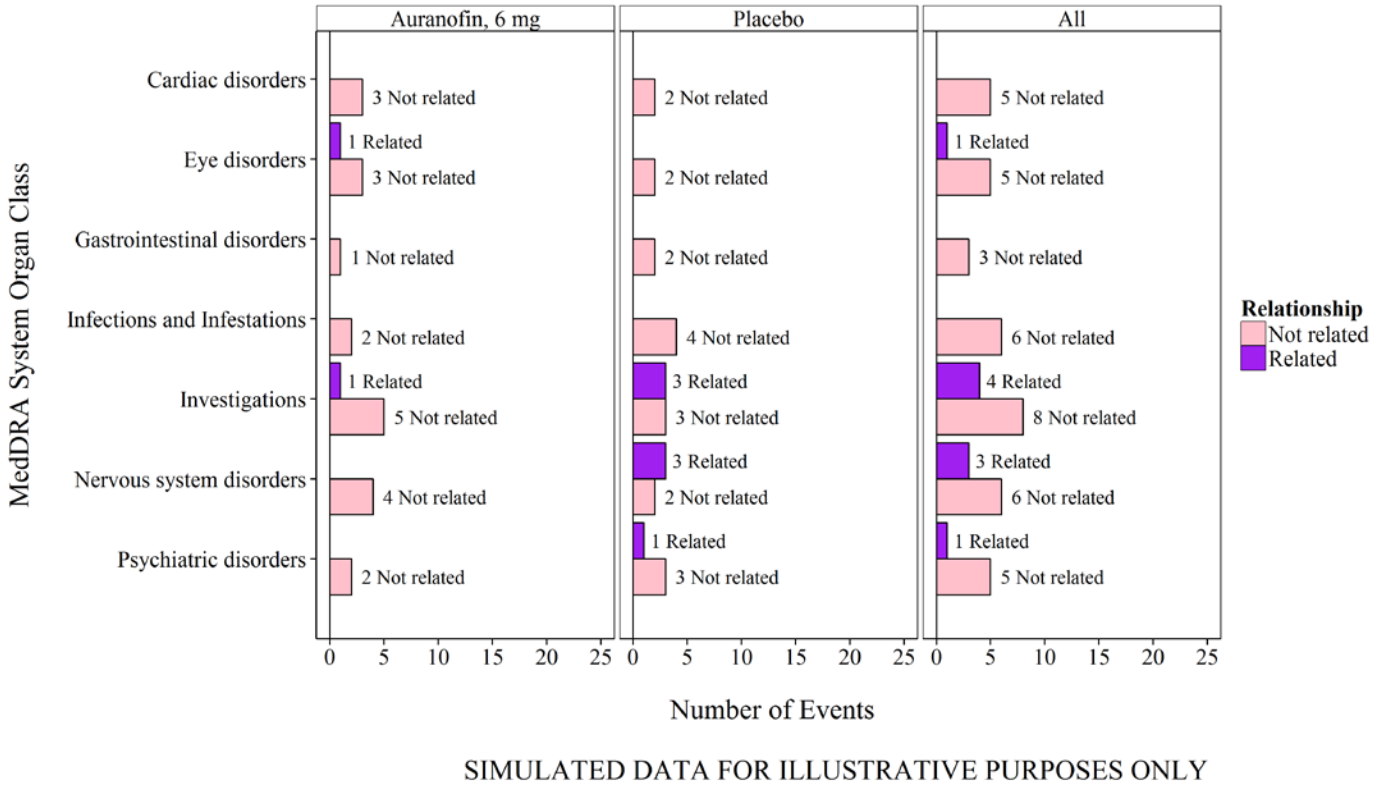
Figure will be repeated for the symptomatic amebiasis group.



SIMULATED DATA FOR ILLUSTRATIVE PURPOSES ONLY

Figure 15: Frequency of Unsolicited Adverse Events by MedDRA System Organ Class and Relationship to Treatment Asymptomatic Giardiasis Group (N=68)

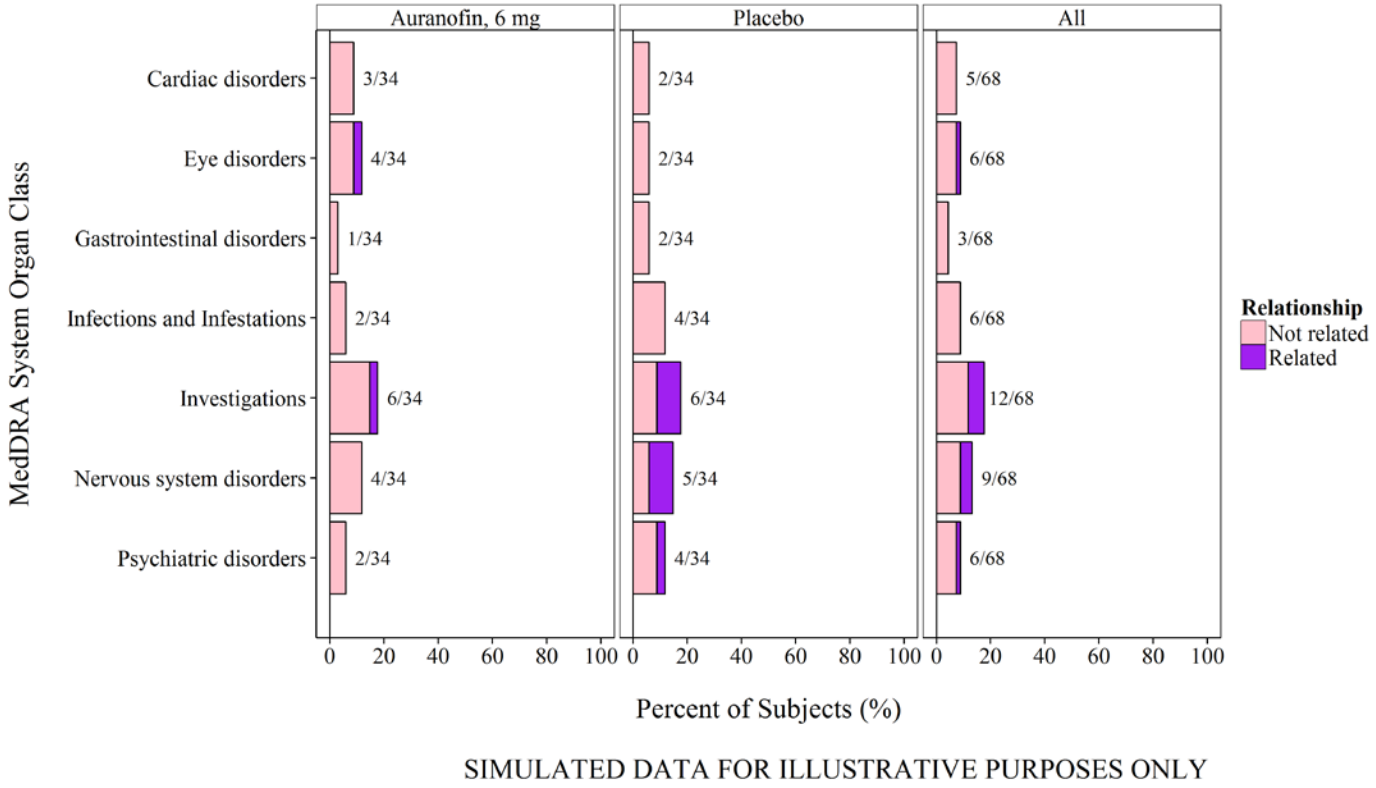
Figure will be repeated for the symptomatic giardiasis group.



SIMULATED DATA FOR ILLUSTRATIVE PURPOSES ONLY

Figure 16: Incidence of Unsolicited Adverse Events by MedDRA System Organ Class and Relationship to Treatment - Asymptomatic Amebiasis Group (N=68)

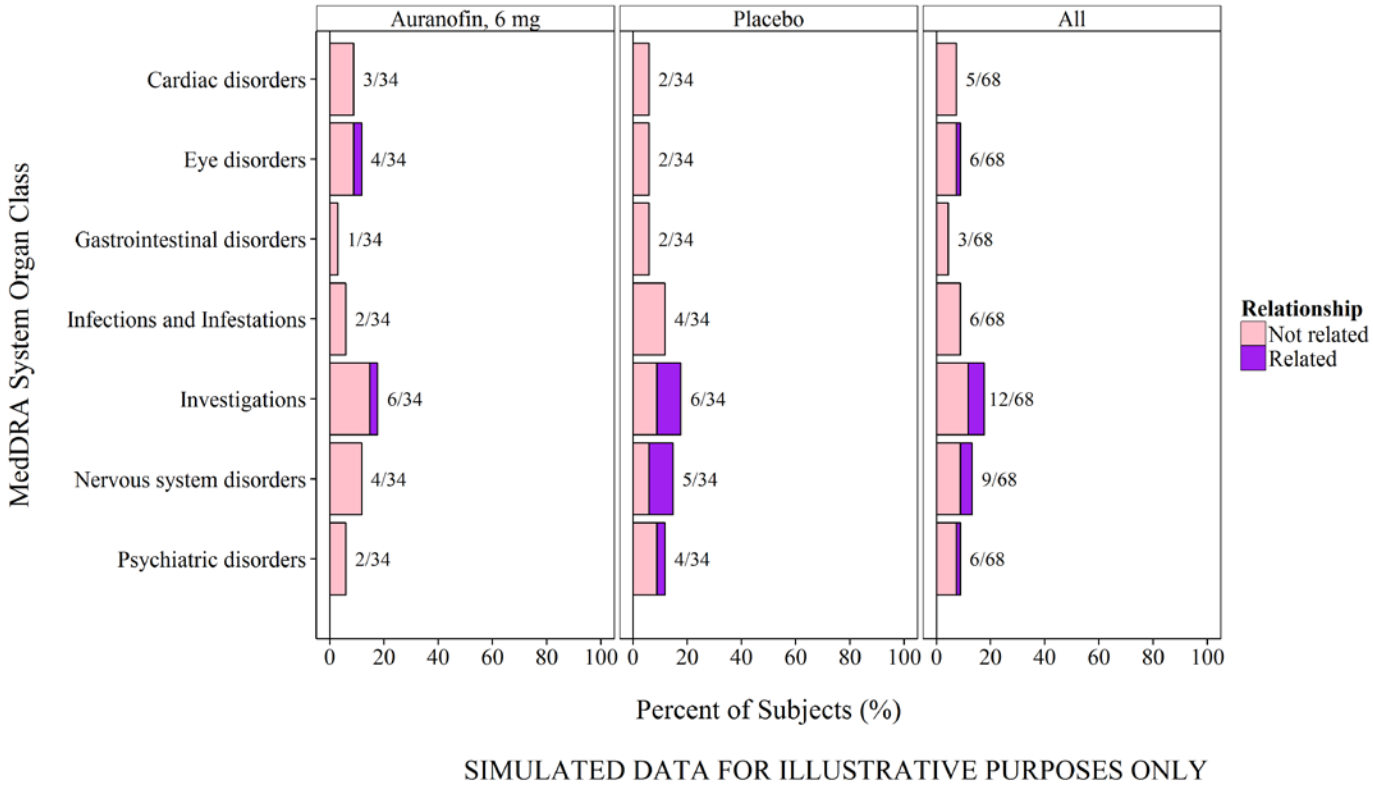
Figure will be repeated for the symptomatic amebiasis group.



SIMULATED DATA FOR ILLUSTRATIVE PURPOSES ONLY

Figure 17: Incidence of Unsolicited Adverse Events by MedDRA System Organ Class and Relationship to Treatment - Asymptomatic Giardiasis Group (N=68)

Figure will be repeated for the symptomatic giardiasis group.



SIMULATED DATA FOR ILLUSTRATIVE PURPOSES ONLY

Figure 18: Frequency of Unsolicited Adverse Events by Relationship to Treatment - Asymptomatic Amebiasis Group (N=68)

Figure will be repeated for the symptomatic amebiasis group.

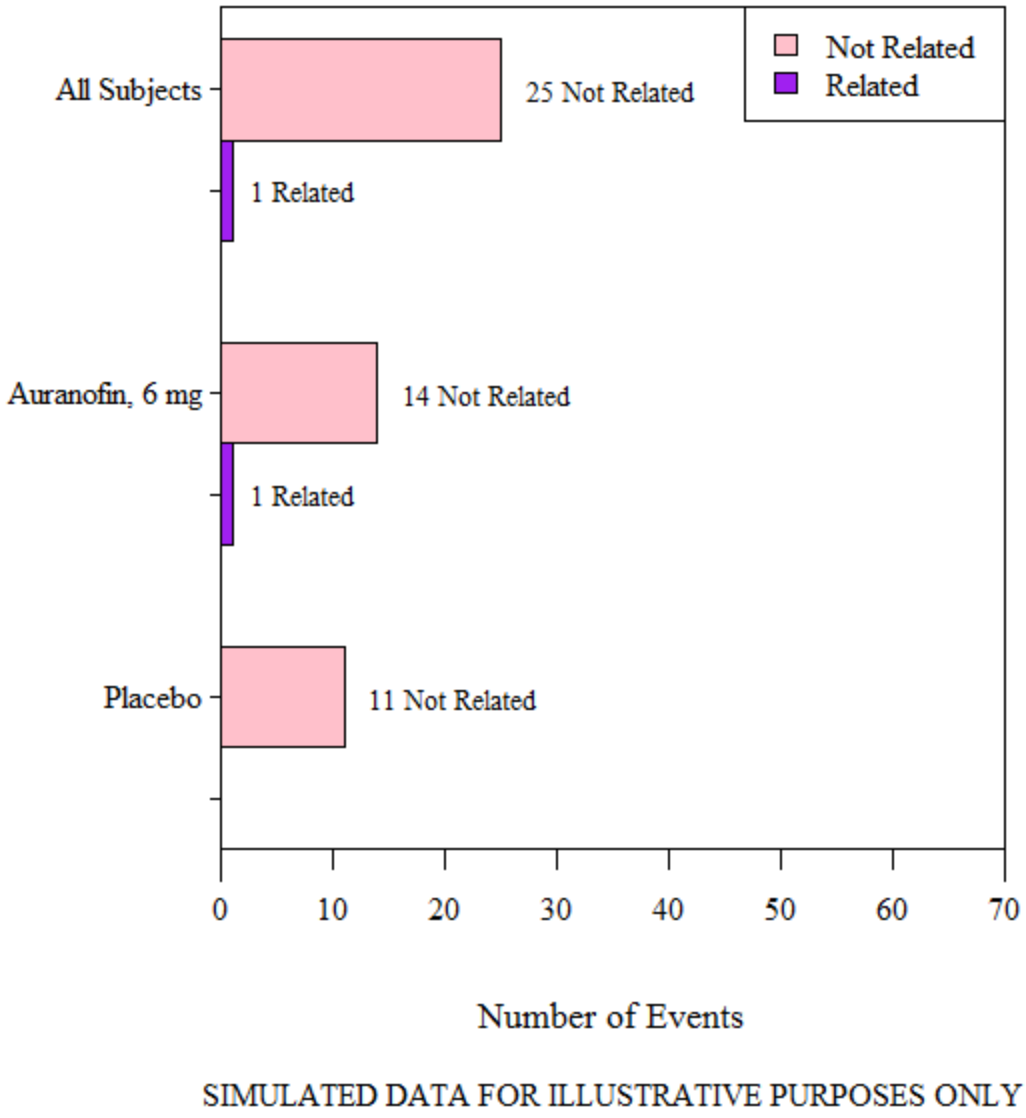


Figure 19: Frequency of Unsolicited Adverse Events by Relationship to Treatment - Asymptomatic Giardiasis Group (N=68)

Figure will be repeated for the symptomatic giardiasis group.

Figure 20: Incidence of Unsolicited Adverse Events by Relationship to Treatment - Asymptomatic Amebiasis Group (N=68)

Figure will be repeated for the symptomatic amebiasis group.

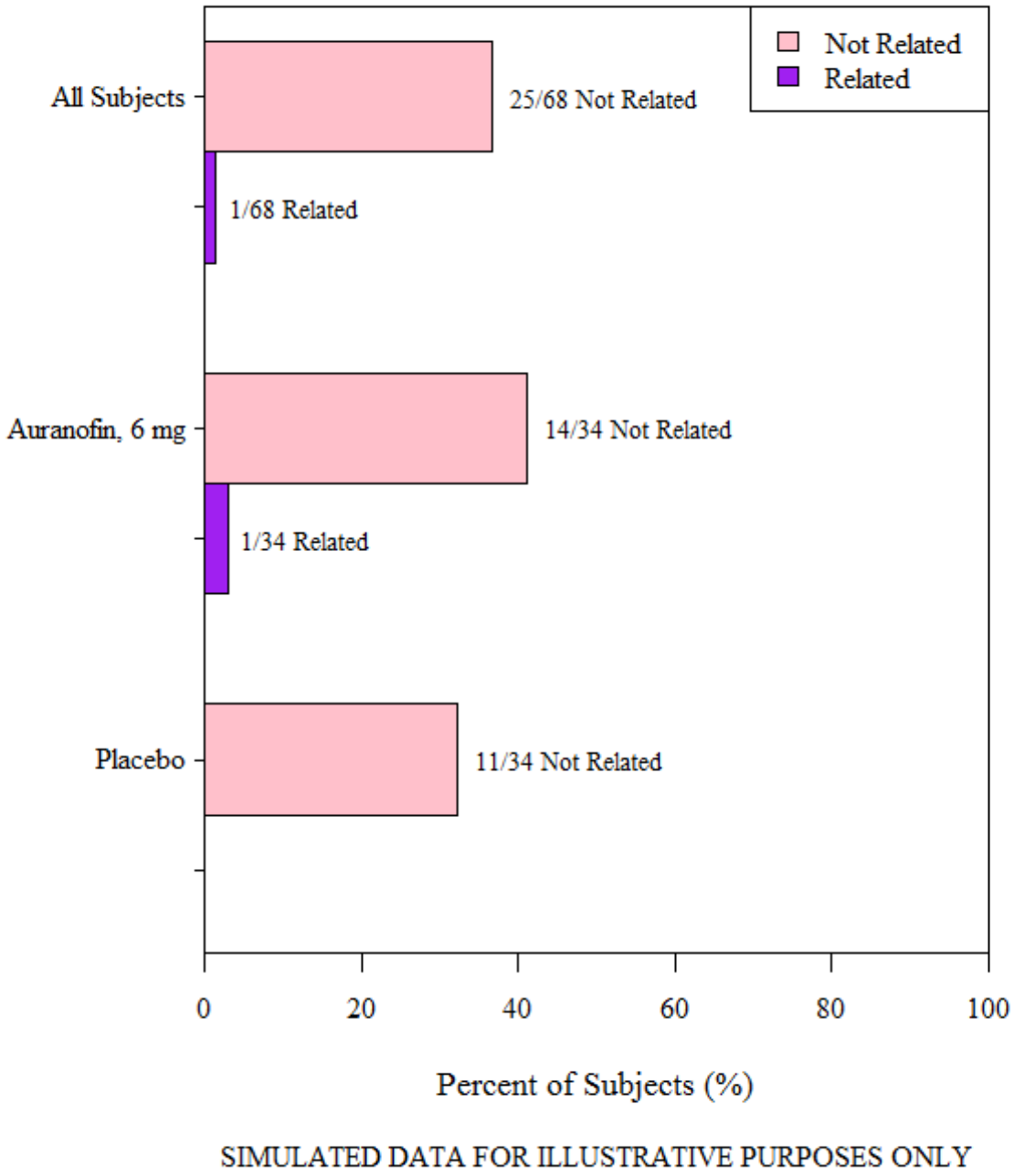
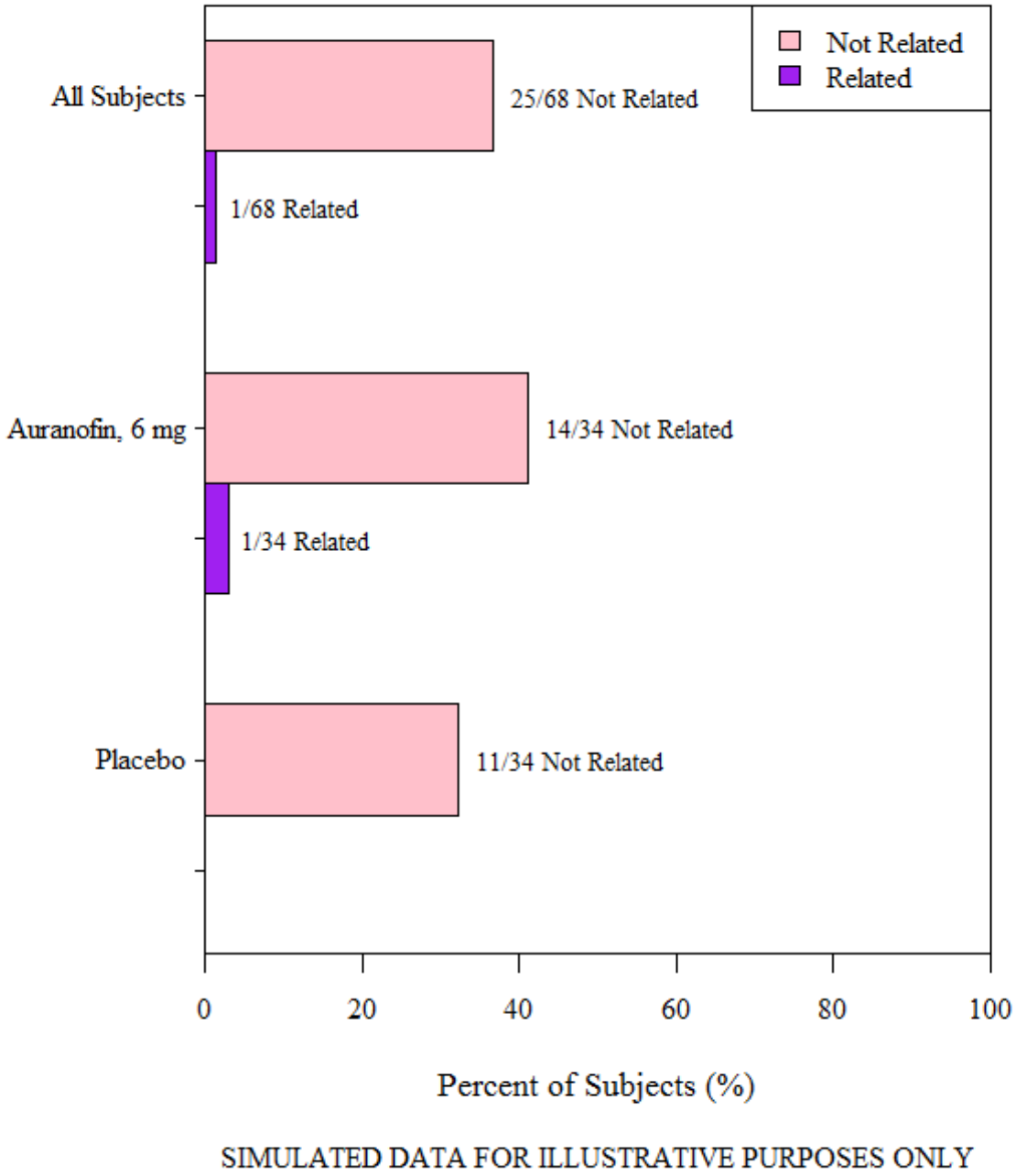


Figure 21: Incidence of Unsolicited Adverse Events by Relationship to Treatment - Asymptomatic Giardiasis Group (N=68)

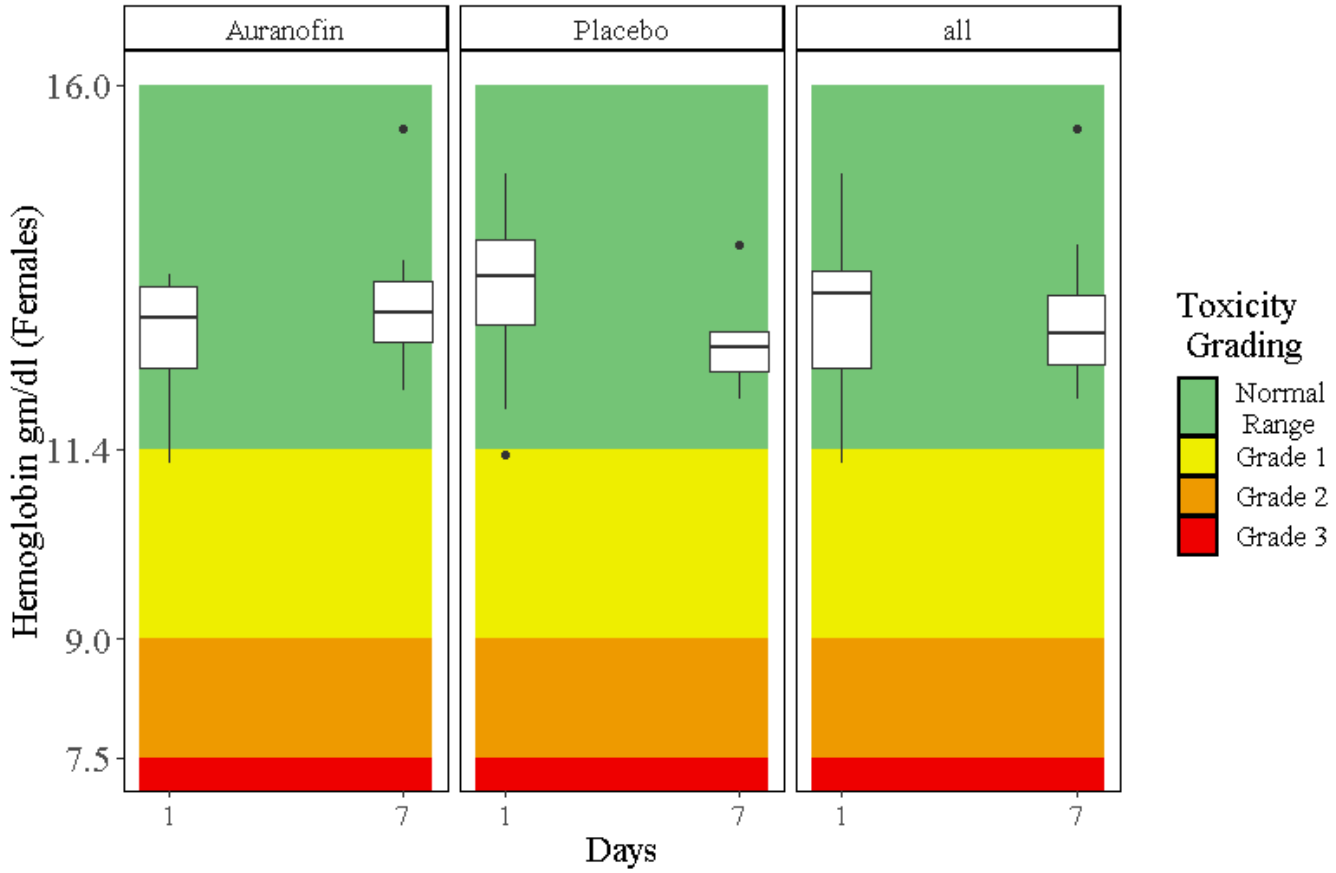
Figure will be repeated for the symptomatic giardiasis group.



14.3.5 Displays of Laboratory Results

Figure 22: Laboratory Results: Distribution on Baseline and Day 7 by Laboratory Parameter, Treatment Group, and Gender (where appropriate) - Asymptomatic Amebiasis Group (N=68)

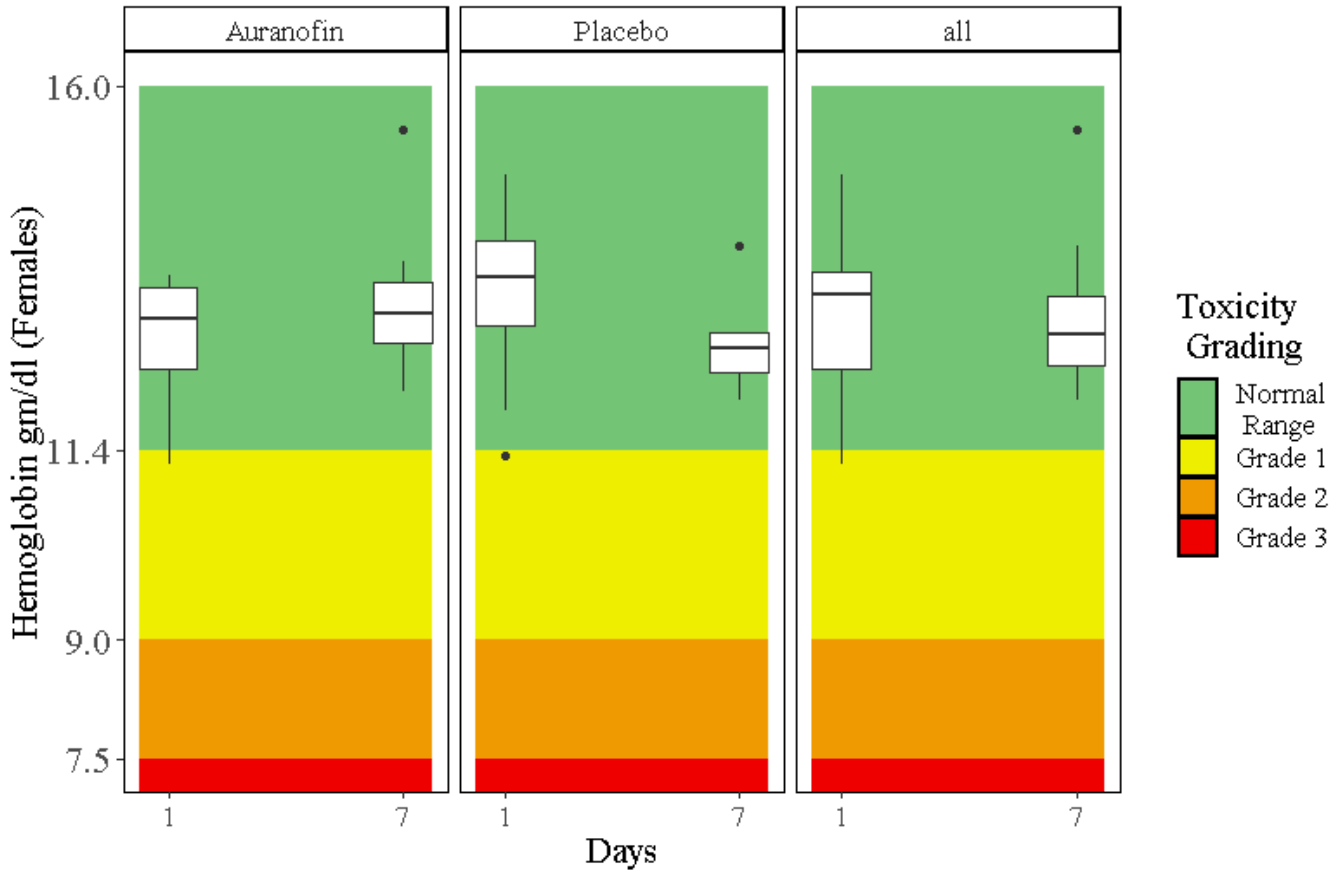
Figure will be repeated for the symptomatic amebiasis group.



Grading criteria were changed during the course of the study. The most conservative grading thresholds will be displayed. Other ranges will be shown as dashed lines or indicated in a footnote.

Figure 23: Laboratory Results: Distribution on Baseline and Day 7 by Laboratory Parameter, Treatment Group, and Gender (where appropriate) - Asymptomatic Giardiasis Group (N=68)

Figure will be repeated for the symptomatic giardiasis group.



Grading criteria were changed during the course of the study. The most conservative grading thresholds will be displayed. Other ranges will be shown as dashed lines or indicated in a footnote.

APPENDIX 3. LISTINGS MOCK-UPS

LISTINGS

16.1.6: Listing of Subjects Receiving Investigational Product

(not included in SAP, but this is a placeholder for the CSR)

16.2 Database Listings by Subject

16.2.1 Discontinued Subjects

Listing 1: 16.2.1.1: Early Terminations or Discontinued Subjects - Asymptomatic Amebiasis Group

Subject ID	Treatment Group	Category	Reason for Early Termination or Treatment Discontinuation	Study Day

Listing 2 : 16.2.1.2: Early Terminations or Discontinued Subjects - Asymptomatic Giardiasis Group

Subject ID	Treatment Group	Category	Reason for Early Termination or Treatment Discontinuation	Study Day

16.2.2 Protocol Deviations

Listing 3: 16.2.2.1: Subject-Specific Protocol Deviations -Asymptomatic Amebiasis Group

Subject ID	Treatment Group	DV Number	Deviation	Deviation Category	Study Day	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Resolution	Comments

Listing will be repeated for the symptomatic study population.

Listing 4: 16.2.2.2: Subject-Specific Protocol Deviations - Asymptomatic Giardiasis Group

Subject ID	Treatment Group	DV Number	Deviation	Deviation Category	Study Day	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Resolution	Comments

Listing will be repeated for the symptomatic study population.

Listing 5: 16.2.2.2.3: Non-Subject-Specific Protocol Deviations -Asymptomatic Amebiasis Group

Site	Deviation	Start Date	End Date	Reason for Deviation	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Category	Deviation Resolution	Comments

Listing will be repeated for the symptomatic study population.

Listing 6: 16.2.2.2.4: Non-Subject-Specific Protocol Deviations - Asymptomatic Giardiasis Group

Site	Deviation	Start Date	End Date	Reason for Deviation	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Category	Deviation Resolution	Comments

Listing will be repeated for the symptomatic study population.

16.2.3 Subjects Excluded from the Efficacy Analysis

Listing 7: 16.2.3.1: Subjects Excluded from Analysis Populations - Asymptomatic Amebiasis Group

Treatment Group	Subject ID	Analyses in which Subject is Included	Analyses from which Subject is Excluded	Results Available?	Reason Subject Excluded
		[e.g., Safety, m-ITT, PP]	[e.g., Safety, m-ITT, PP]		
Note: "Yes" in the "Results available" column indicates that available data were removed from the analysis. "No" indicates that no data were available for inclusion in the analysis.					

Listing will be repeated for the symptomatic study population

Listing 8: 16.2.3.2: Subjects Excluded from Analysis Populations - Asymptomatic Giardiasis Group

Treatment Group	Subject ID	Analyses in which Subject is Included	Analyses from which Subject is Excluded	Results Available?	Reason Subject Excluded
		[e.g., Safety, m-ITT, PP]	[e.g., Safety, m-ITT, PP]		
Note: "Yes" in the "Results available" column indicates that available data were removed from the analysis. "No" indicates that no data were available for inclusion in the analysis.					

Listing will be repeated for the symptomatic study population.

16.2.4 Demographic Data

Listing 9: 16.2.4.1: Demographic Data - Asymptomatic Amebiasis Group

Subject ID	Treatment Group	Sex	Age at Enrollment (years)	Ethnicity	Race

Listing will be repeated for the symptomatic study population.

Listing 10: 16.2.4.2: Demographic Data - Asymptomatic Giardiasis Group

Subject ID	Treatment Group	Sex	Age at Enrollment (years)	Ethnicity	Race

Listing will be repeated for the symptomatic study population.

Listing 11: 16.2.4.3: Pre-Existing Medical Conditions - Asymptomatic Amebiasis Group

Subject ID	Treatment Group	MH Number	Medical History Term	Condition Start Day	Condition End Day	MedDRA System Organ Class	MedDRA Preferred Term

Listing will be repeated for the symptomatic study population.

Listing 12: 16.2.4.4: Pre-Existing Medical Conditions - Asymptomatic Giardiasis Group

Subject ID	Treatment Group	MH Number	Medical History Term	Condition Start Day	Condition End Day	MedDRA System Organ Class	MedDRA Preferred Term

Listing will be repeated for the symptomatic study population.

16.2.5 Compliance and/or Drug Concentration Data (if available)

Listing 13: 16.2.5.1: Compliance and/or Drug Concentration Data - Asymptomatic Amebiasis Group

Subject ID	Treatment Group	Dose(s) Missed
		[e.g., Day 3, Day 5, etc.]

Listing will be repeated for the symptomatic study population.

Listing 14: 16.2.5.2: Compliance and/or Drug Concentration Data - Asymptomatic Giardiasis Group

Subject ID	Treatment Group	Dose(s) Missed
		[e.g., Day 3, Day 5, etc.]

Listing will be repeated for the symptomatic study population.

16.2.6 Individual Efficacy/Immunogenicity Response Data

Listing 15: 16.2.6.1: Listing of Efficacy Endpoints - Asymptomatic Amebiasis Group

Treatment Group	Subject ID	Study Day	Parasite Load (parasites/uL)	Antigen Test	Wet mount result	Trichrome staining	Parasitological Response (no detection of cysts or trophozoites or a negative antigen test)	Relapse (Strain genetically matches Day 1 strain)*	Reinfection (Strain genetically matches Day 1 strain)*
*Yes, no, or NA if no parasites are detected on the specified day.									

Listing 16: 16.2.6.2: Listing of Efficacy Endpoints - Symptomatic Amebiasis Group

Treatment Group	Subject ID	Study Day	Diarrhea	Parasite Load (parasites/uL)	Antigen Test	Wet mount	Trichrome staining	Parasitological Response (no detection trophozoites by microscopy)	Relapse (Strain genetically matches Day 1 strain)*	Reinfection (Strain genetically matches Day 1 strain)*
*Yes, no, or NA if no parasites are detected on the specified day.										

Listing 17: 16.2.6.3: Listing of Efficacy Endpoints - Asymptomatic Giardiasis Group

Treatment Group	Subject ID	Study Day	Parasite Load (parasites/uL)	Antigen Test	Wet mount	Trichrome staining	Parasitological Response (no detection of cysts or trophozoites or a negative antigen test)	Relapse (Strain genetically matches Day 1 strain)*	Reinfection (Strain genetically matches Day 1 strain)*
*Yes, no, or NA if no parasites are detected on the specified day.									

Listing 18: 16.2.6.4: Listing of Efficacy Endpoints - Symptomatic Giardiasis Group

Treatment Group	Subject ID	Study Day	Diarrhea	Parasite Load (parasites/uL)	Antigen Test	Wet mount	Trichrome staining	Parasitological Response (no detection trophozoites by microscopy)	Relapse (Strain genetically matches Day 1 strain)*	Reinfection (Strain genetically matches Day 1 strain)*
*Yes, no, or NA if no parasites are detected on the specified day										

16.2.7 Adverse Events

Listing 19: 16.2.7.1.1: Solicited Events - Asymptomatic Amebiasis Group – First listing

Subject ID	Treatment Group	Number of doses received	Study Day	Loose stools or diarrhea	Abdominal Pain	Nausea with or without vomiting	Constipation	Anorexia	Flatulence	Dyspepsia	Dysgeusia
				[severity]	[severity]	[severity]	[severity]				

* MA = Data reported by subject on the Memory Aid and reviewed by clinic staff and reported in Solicited Events eCRF.
Clinic = Data collected by clinic staff during physical exam or symptom assessment (treatment administration record, in-clinic assessment, etc.)

Listing 20: 16.2.7.1.2: Solicited Events - Asymptomatic Amebiasis Group – Second listing

Subject ID	Treatment Group	Number of doses received	Study Day	Pruritus	Hair loss	Urticaria	Stomatitis	Conjunctivitis	Glossitis	Hematuria	Rash
				[severity]	[severity]	[severity]	[severity]				

* MA = Data reported by subject on the Memory Aid and reviewed by clinic staff and reported in Solicited Events eCRF.
Clinic = Data collected by clinic staff during physical exam or symptom assessment (treatment administration record, in-clinic assessment, etc.)

Listing will be repeated for the symptomatic study population but will omit diarrhea.

Listing 21: 16.2.7.1.2: Solicited Events - Asymptomatic Giardiasis Group – First listing

Subject ID	Treatment Group	Number of doses received	Study Day	Loose stools or diarrhea	Abdominal Pain	Nausea with or without vomiting	Constipation	Anorexia	Flatulence	Dyspepsia	Dysgeusia
				[severity]	[severity]	[severity]	[severity]				

* MA = Data reported by subject on the Memory Aid and reviewed by clinic staff and reported in Solicited Events eCRF.
Clinic = Data collected by clinic staff during physical exam or symptom assessment (treatment administration record, in-clinic assessment, etc.)

Listing 22: 16.2.7.1.3: Solicited Events Asymptomatic Giardiasis Group – Second listing

Subject ID	Treatment Group	Number of doses received	Study Day	Pruritus	Hair loss	Urticaria	Stomatitis	Conjunctivitis	Glossitis	Hematuria	Rash
				[severity]	[severity]	[severity]	[severity]				

* MA = Data reported by subject on the Memory Aid and reviewed by clinic staff and reported in Solicited Events eCRF.
Clinic = Data collected by clinic staff during physical exam or symptom assessment (treatment administration record, in-clinic assessment, etc.)

Listing will be repeated for the symptomatic study population but will omit diarrhea.

Listing 23: 16.2.7.2.1: Unsolicited Adverse Events - Asymptomatic Amebiasis Group

Adverse Event	Associated with Dose No.	No. of Days Post Associated Dose (Duration)	Severity	SAE?	Relationship to Study Treatment	In Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Treatment Group: , Subject ID: , AE Number:											
Comments:											
Treatment Group: , Subject ID: , AE Number:											
Comments:											
Note: For additional details about SAEs, see Table: xx.											

Listing will be repeated for the symptomatic study population.

Listing 24: 16.2.7.2.2: Unsolicited Adverse Events - Asymptomatic Giardiasis Group

Adverse Event	Associated with Dose No.	No. of Days Post Associated Dose (Duration)	Severity	SAE?	Relationship to Study Treatment	In Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Treatment Group: , Subject ID: , AE Number:											
Comments:											
Treatment Group: , Subject ID: , AE Number:											
Comments:											
Note: For additional details about SAEs, see Table: xx.											

Listing will be repeated for the symptomatic study population.

16.2.8 Individual Laboratory Measurements

Listing 25: 16.2.8.1.1: Clinical Laboratory Results: Hematology - Asymptomatic Amebiasis Group

Subject ID	Treatment Group	Sex	Age (years)	Planned Time Point	Actual Study Day	White Blood Cells (10^9/L)	Hemoglobin (g/dL)	Hematocrit (% Decrease from baseline)	Platelets (10^9/L)

Listing 26: 16.2.8.1.2: Clinical Laboratory Results: Hematology - Asymptomatic Giardiasis Group

Subject ID	Treatment Group	Sex	Age (years)	Planned Time Point	Actual Study Day	White Blood Cells (10^9/L)	Hemoglobin (g/dL)	Hematocrit (% Decrease from baseline)	Platelets (10^9/L)

Listings will be repeated for the symptomatic study population.

Listing 27: 16.2.8.2.1: Clinical Laboratory Results: Biochemistry - Asymptomatic Amebiasis Group

Subject ID	Treatment Group	Sex	Age (years)	Planned Time Point	Actual Study Day	Blood Urea Nitrogen (mg/dL)	Creatinine (mg/dL)	Aspartate Aminotransferase (IU/L)	Alanine Aminotransferase (IU/L)

Listing 28: 16.2.8.2.2: Clinical Laboratory Results: Biochemistry - Asymptomatic Giardiasis Group

Subject ID	Treatment Group	Sex	Age (years)	Planned Time Point	Actual Study Day	Blood Urea Nitrogen (mg/dL)	Creatinine (mg/dL)	Aspartate Aminotransferase (IU/L)	Alanine Aminotransferase (IU/L)

Listings will be repeated for the symptomatic study population.

Listing 29: 16.2.8.3.1: Clinical Laboratory Results: Urinalysis - Asymptomatic Amebiasis Group

Subject ID	Treatment Group	Sex	Age (years)	Planned Time Point	Actual Study Day	Protein

Listing 30: 16.2.8.3.2: Clinical Laboratory Results: Urinalysis - Asymptomatic Giardiasis Group

Subject ID	Treatment Group	Sex	Age (years)	Planned Time Point	Actual Study Day	Protein

Listings will be repeated for the symptomatic study population.

16.2.9 Vital Signs and Physical Exam Findings

Listing 31: 16.2.9.1.1: Vital Signs - Asymptomatic Amebiasis Group

Subject ID	Treatment Group	Planned Time Point	Actual Study Day	Temperature (°C)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (beats/min)	Respiratory Rate (breaths/min)	Weight (kg)	Height (cm)

Listing 32: 16.2.9.1.2: Vital Signs - Asymptomatic Giardiasis Group

Subject ID	Treatment Group	Planned Time Point	Actual Study Day	Temperature (°C)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (beats/min)	Respiratory Rate (breaths/min)	Weight (kg)	Height (cm)

Listings will be repeated for the symptomatic study population.

Listing 33: 16.2.9.2.1: Physical Exam Findings - Asymptomatic Amebiasis Group

Subject ID	Treatment Group	Planned Time Point	Actual Study Day	Body System	Abnormal Finding	Reported as an AE? (AE Number)

Listing 34: 16.2.9.2.2: Physical Exam Findings - Asymptomatic Giardiasis Group

Subject ID	Treatment Group	Planned Time Point	Actual Study Day	Body System	Abnormal Finding	Reported as an AE? (AE Number)

Listings will be repeated for the symptomatic study population.

16.2.10 Concomitant Medications

Listing 35: 16.2.10.1: Concomitant Medications - Asymptomatic Amebiasis Group

Subject ID	Treatment Group	CM Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for an AE? (AE Number)	Taken for a condition on Medical History? (MH Number)

Listing 36: 16.2.10.2: Concomitant Medications - Asymptomatic Giardiasis Group

Subject ID	Treatment Group	CM Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for an AE? (AE Number)	Taken for a condition on Medical History? (MH Number)

Listings will be repeated for the symptomatic study population.

16.2.11.1 Pregnancy Reports

Listing 37: 16.2.11.1.1: Pregnancy Reports - Maternal Information

Subject ID	Study population and disease group	Treatment Group	Pregnancy Number	Study Day Corresponding to Estimated Date of Conception	Source of Maternal Information	Pregnancy Status	Mother's Pre-Pregnancy BMI	Mother's Weight Gain During Pregnancy	Tobacco, Alcohol, or Drug Use During Pregnancy?	Medications During Pregnancy?	Maternal Complications During Pregnancy?	Maternal Complications During Labor, Delivery, or Post-Partum?
	Symptomatic giardiasis											

Note: Maternal Complications are included in the Adverse Event listing. Medications taken during pregnancy are included in the Concomitant Medications Listing.

Listing 38: 16.2.11.1.2: Pregnancy Report - Gravida and Para

				Live Births												
Subject ID	Study population and disease group	Pregnancy Number	Gravida	Extremely Preterm Births	Very Preterm Births	Early Preterm Births	Late Preterm Births	Early Term Births	Full Term Births	Late Term Births	Post Term Births	Still Births	Spontaneous Abortion/ Miscarriage	Elective Abortions	Therapeutic Abortions	Major Congenital Anomaly with Previous Pregnancy?

Note: Gravida includes the current pregnancy, para events do not.

16.2.11.2: Pregnancy Reports – Gravida and Para

Listing 39: 16.2.11.2.1: Pregnancy Reports – Live Birth Outcomes

Subject ID	Study population and disease group	Pregnancy Number	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Live Birth	Size for Gestational Age	Apgar Score, 1 minute	Apgar Score, 5 minutes	Cord pH	Congenital Anomalies?	Illnesses/ Hospitalizations within 1 Month of Birth?

Note: Congenital Anomalies are included in the Adverse Event listing.

Listing 40: 16.2.11.2.2: Pregnancy Reports – Still Birth Outcomes

Subject ID	Study population and disease group	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Still Birth	Size for Gestational Age	Cord pH	Congenital Anomalies?	Autopsy Performed?	If Autopsy, Etiology for Still Birth Identified?

Listing 41: 16.2.11.2.3: Pregnancy Reports - Spontaneous, Elective, or Therapeutic Abortion Outcomes

Subject ID	Study population and disease group	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Gestational Age at Termination	Abnormality in Product of Conception?	Reason for Therapeutic Abortion