A Randomized, Double-Blind Placebo-Controlled Phase I Trial Evaluating the Safety and Pharmacokinetics of Oxfendazole

DMID Protocol Number: 12-0053

DMID Funding Mechanism: Contract # HHSN272200800008C

IND Sponsor: Division of Microbiology and Infectious Diseases

The National Institute of Allergy and Infectious Diseases

The National Institutes of Health

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Version Number: 5.0

September 1, 2015

STATEMENT OF COMPLIANCE

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

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

All individuals responsible for the design and conduct of this study have completed Human Subjects Protection Training and are qualified to be conducting this research prior to the enrollment of any subjects. Curricula vitae for all investigators and sub investigators participating in this trial are on file in a central facility (21 CFR 312.23 [a] [6] [iii] [b] edition).

SIGNATURE PAGE

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

Site Principal Investigator: _____
Name/Title (Print)

Signature: _____

Date: _____

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC_{0-t}	Area Under the Curve to the Final Sample
AUC_{∞}	Area Under the Curve to Infinity
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drugs Evaluation and Research
CFR	Code of Federal Regulations
CL/F	Oral Clearance
C_{max}	Maximum Plasma Concentration
CNS	Central Nervous System
CRF	Case Report Form
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
eCRF	Electronic Case Report Form
EKG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
IV	Intravenous
λ_z	Elimination Rate Constant
LOQ	Limits of Quantitation
LLN	Lower Limit of Normal
MedDRA ®	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NF	National Formulary
NEJM	New England Journal of Medicine
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
NOEL	No Observed Effect Level

OHRP	Office for Human Research Protections
OHSR	Office for Human Subjects Research
ORA	Office of Regulatory Affairs, DMID, NIAID, NIH, DHHS
OXF	Oxfendazole
PHI	Personal Health Information
PI	Principal Investigator
PK	Pharmacokinetics
SAE	Serious Adverse Event
SDCC	Statistical and Data Coordinating Center
SMC	Safety Monitoring Committee
SRC	Safety Review Committee
$t_{1/2}$	Elimination Half-life
TBL	Total Bilirubin
T_{max}	Time to C_{max}
ULN	Upper Limit of Normal
US	United States
USP	United States Pharmacopeia
VTEU	Vaccine Treatment and Evaluation Unit
V_Z/F	Oral Volume of Distribution

PROTOCOL SUMMARY

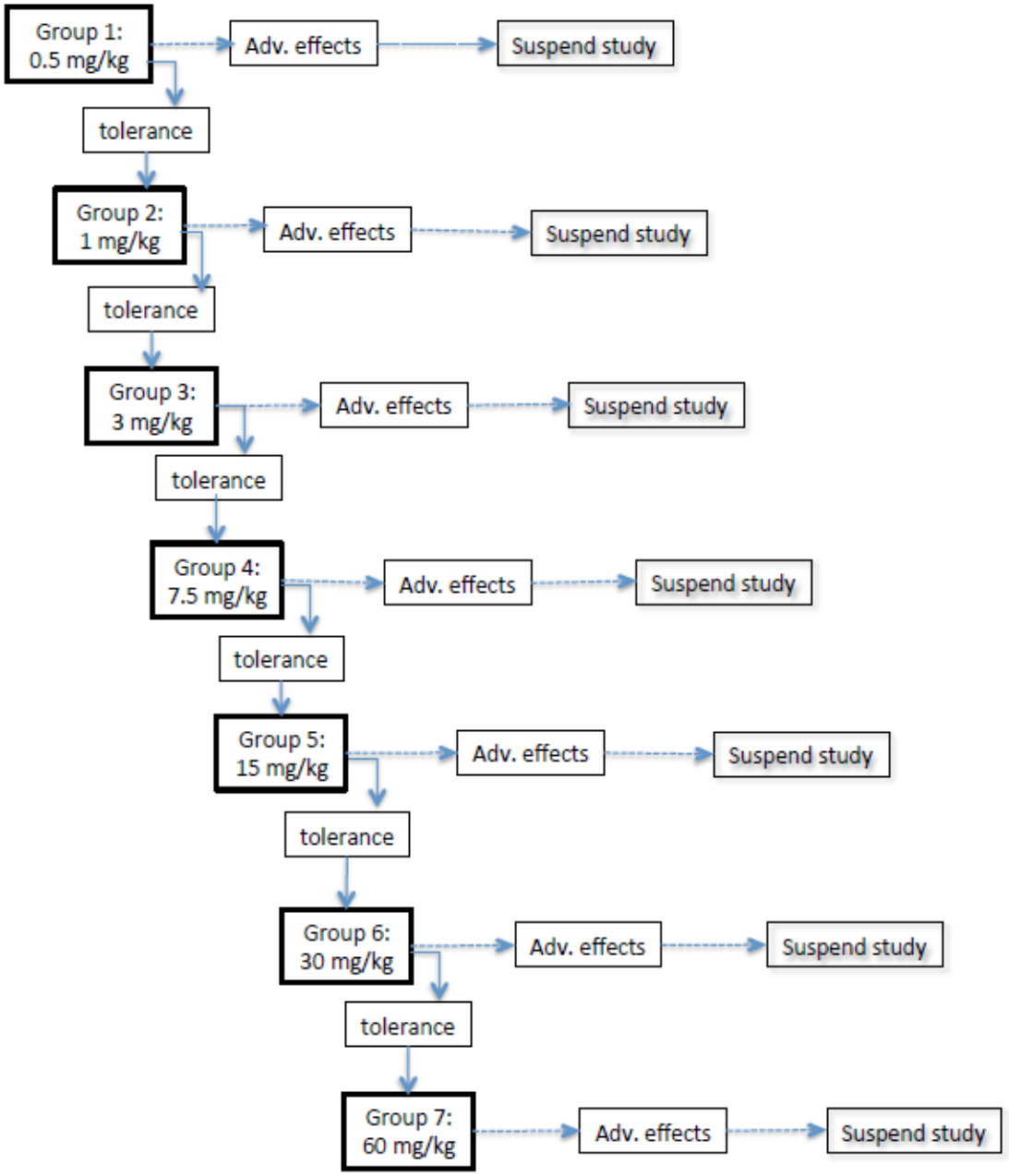
Title:	A Randomized, Double-Blind Placebo-Controlled Phase I Trial Evaluating the Safety and Pharmacokinetics of Oxfendazole
Phase:	I
Population:	Up to 70 healthy males and females (non-childbearing potential), ages 18-45, recruited from around the University of Iowa
Number of Sites:	One site, the University of Iowa
Study Duration:	Approximately 18 months
Subject Participation Duration:	2 weeks
Description of Agent or Intervention:	Single oral dose of an aqueous suspension of oxfendazole, a benzimidazole carbamate antiparasitic drug.
Objectives:	**Primary:** • Assess the safety and tolerability of oxfendazole in healthy adults. **Secondary:** • Assess the pharmacokinetic profile of oxfendazole • Assess the metabolism of oxfendazole
Endpoints/Outcome Measures:	**Primary endpoint:** 1. The rate of adverse events (AEs) related to oxfendazole within 14 days of receipt of a single oral dose. **Secondary endpoints:** 1. Plasma Cmax, Tmax, AUC , $t_{1/2}$ of oxfendazole for each dosage group. 2. Plasma and urine concentrations of oxfendazole fenbendazole and oxfendazole sulfone at time points specified in Appendix A Schedule of Events and described in Section 4 Study Design relative to oral

dosing.

Description of Study Design:	This Phase I study is a randomized, double-blind, placebo-controlled evaluation of the safety and pharmacokinetics of escalating single oral doses of oxfendazole (0.5 to 60 mg/kg) in healthy volunteers. Up to 70 volunteers will participate in this study. The dose will be increased approximately three-fold (one-half log) at each increment, and each cohort will comprise 10 volunteers (8 subjects will receive study drug and 2 will receive placebo). Two sentinel subjects (1 drug/1 placebo) in each cohort will be monitored for 48 hours after receiving the study drug prior to completing enrollment in the cohort. Subjects will be monitored for two weeks after dosing, including monitoring the pharmacokinetics and metabolism of oxfendazole in blood and urine. Each new cohort will be dosed only after the two week safety data for the preceding group have been reviewed. If a clinically significant AE is observed, and if this event is drug-related the safety monitoring committee will be convened to determine whether the study should continue.
Estimated Time to Complete Enrollment:	17 months

Schematic of Study Design:

Note: Two sentinel subjects will receive the study product (1 drug/1 placebo) in each group and be monitored 48 hours for adverse events prior to completing enrollment of the remaining 8 subjects in the group. Adverse events assessed as related to the study product and as defined in the Halting Rules may result in suspension of the study.



1 KEY ROLES

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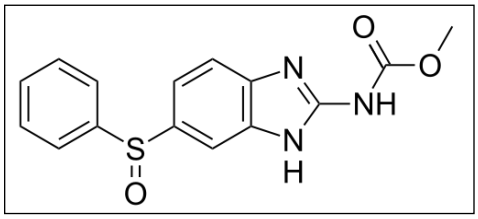
2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

In humans, cerebral cysticercosis is the most common parasitosis of the central nervous system (CNS) (1, 2). On a worldwide basis, approximately 50,000 people die each year because of neurocysticercosis (3), and it is estimated that 1000 cases occur annually in the United States (US).(4) The current treatment for neurocysticercosis is far from ideal: complete cure is achieved in approximately 50% of cases, with regimens that require multiple doses of drug over several weeks (1, 5-7). Oxfendazole is currently marketed for use against lungworms and enteric helminths in beef livestock. In preliminary studies in pigs, single oral doses of oxfendazole appear to have substantial activity against the tissue stages of *Taenia solium* (cysticercosis) (8-10). These data suggest that oxfendazole has the potential to be useful as a single dose oral treatment for neurocysticercosis. The studies described in this protocol propose the first evaluation in humans of the safety, metabolism, and pharmacokinetics (PK) of oxfendazole.

2.1.1 Oxfendazole

2.1.1.1 Structure and Formulation



Oxfendazole, or [5-(phenylsulphinyl)-1H-benzimidazole-2-yl]carbamic acid methyl ester (Synanthic®), was first identified in the laboratories of Syntex Research, Palo Alto, California, and shown to have anthelminthic properties against larval and adult forms of gastrointestinal cestodes and nematodes in various animal species (11). The structure consists of the benzimidazole carbamate characteristic of this group of drugs, with a phenylsulphinyl substituent in position 5 (12). The currently available formulation is an aqueous suspension of either 9.06% or 22.5% oxfendazole (Synanthic®), manufactured by Boehringer Ingelheim Animal Health. Aliquots of the commercially available suspension will be used in the present study, as described in Table 3 below. Synanthic® should be stored at temperatures not to exceed 104°F (40°C) and protected from freezing and excessive heat (13, 14).

2.1.1.2 History

The introduction of thiabendazole as the first benzimidazole anthelminthic in the early 1960s provided a significant advance in veterinary antiparasitic treatment (15). However, thiabendazole has a short biological half-life, due to rapid hydroxylation of the 5 (6) position of the benzimidazole ring and extensive urinary clearance (16). Further efforts were directed

toward the production of compounds with a variety of substitutions in this metabolically labile position, leading to different pharmacological behavior, and increased potency and spectrum of antiparasitic activity (17). The more potent later generations of benzimidazoles include fenbendazole, oxfendazole, and albendazole, with efficacy against roundworms, tapeworms, and even parasites residing outside the gastrointestinal tract (18). Thiabendazole, mebendazole and albendazole are currently approved and marketed in the US for treatment of helminth infections in humans.

2.1.1.3 Mechanism of Action

Benzimidazoles appear to have multiple molecular mechanisms of action. They interfere with bioenergetics in the parasite by inhibiting glucose transport and the fumarate reductase reaction, as well as restricting glucose uptake (18). They also alter the tubulin-microtubule equilibrium, by binding at the colchicine site in the tubulin dimer (19). Inhibition of tubulin polymerization induces disintegration of the microtubular network in parasites (20).

2.1.1.4 Prediction of Human No Effect Dose from Chronic Toxicology and Carcinogenicity Studies

No effect dose in chronic preclinical toxicology studies

Oxfendazole has been evaluated in numerous safety and toxicology studies in ruminants as well as in more traditional preclinical species. The results of the most important chronic toxicology studies, with doses adjusted for surface area, are summarized and projected to human doses below.

Table 1. Calculated no effect dose in humans based on outcomes from preclinical toxicology studies

Species	Study	No Effect Dose			
		Preclinical toxicology studies			Calculated adult human equivalent
		Syntex study number(21)	mg/kg/day	mg/m^2/day	mg/kg/day
Mouse	18 mo carcinogenicity	66-M-84	150	375	9.91
Rat	1 yr chronic toxicity	101-R-74	0.7	4.73	0.13
	2 yr carcinogenicity	53-R-83	0.7	4.73	0.13
Dog	1 yr chronic toxicity	18-D-84	13.5	265	7.00
Rat	14 d sub-acute toxicity	xxx	5		0.8
Mouse	Single dose	xxx	6400		512
Rat	Single dose	xxx	3200		512

Species	Study	No Effect Dose	
Dog	Single dose	1600	864

Selection of Starting Dose for Human Phase I study administering a single dose of oxfendazole

Extrapolating (using a body surface area calculation) from the results of *chronic* oxfendazole toxicology studies conducted in animals, the most conservative estimate of a no-effect dose for humans (based on a no observed effect level NOEL] derived from a 1-year study) is 0.13 mg/kg (see Table 1 above). Based on a standard 10-fold safety factor from the No Observed Adverse Effect Level (NOAEL) from single dose studies in the most sensitive species, starting doses up to 50 mg/kg would be supported. Because this exceeds the anticipated therapeutic dose, and due to the lower NOAEL human equivalent dose of 0.8 mg/kg/d seen in rats in the 14d repeat dose a significantly greater safety margin was incorporated. Thus, 1.0 mg/kg has been selected as the starting point for the present single dose Phase I study. Furthermore, since the principal toxicology target organs appear to be the bone marrow and liver, safety monitoring for the proposed Phase I study includes clinical chemistry indicators of bone marrow and liver function.

2.1.1.5 Animal Safety

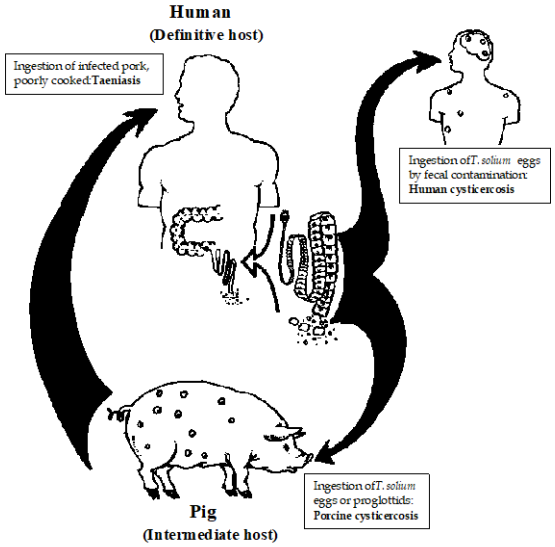
The potential cardiovascular or toxicity effects of oxfendazole (OXF) were investigated after drug administration to beagle dogs (22). Following administration of single oral doses of oxfendazole at 0, 5, 25 or 100 mg/kg, no changes in body weight, body temperature, clinical laboratory evaluations (hematology, serum chemistry, and coagulation studies), changes in vital signs (blood pressure, heart rate) or changes in electrocardiogram evaluations were noted.

A two week toxicology study of oxfendazole administered orally to rats at doses from 0-200 mg/kg, was recently performed (23). There were no changes in feeding, behavior or physiological measurements (23). Animals in the highest dose groups were euthanized on day 8 because of severe toxicity and mortality. Females had a higher incidence of mortality and more severe adverse effects than did males administered the same dose; correspondingly higher OXF exposure was found in females than in males. At the higher doses, WBC depletion was dose related, being severe in females at the highest dose. WBC recovered when OXF administration was suspended. Target organs of toxicity were bone marrow, epididymis, liver, spleen, testis and thymus. Hepatic midzonal fatty change was present in male and female rats administered the higher doses; these changes were still present after a 14-day recovery period. However, no effects on liver enzymes were seen in the clinical chemistry results, suggesting that these effects did not result in overt hepatotoxicity or compromised hepatic function; therefore, the toxicologic significance of this observation is unclear.

Several toxicology studies were performed at the time of Synanthic® approval. In single dose toxicology studies in mice, rats and dogs. One rat that received a dose of 6400 mg/kg, orally died from enteropathy. In subchronic toxicology studies in which rats and dogs were dosed over a two week period at doses ranging from 11-200 mg/kg, orally, decreases in neutrophil count, hemoglobin and hematocrit were seen at the higher doses, as were pathological changes in the liver (with hepatocyte vacuolation), gastroenteropathy, testes, bone marrow, liver, spleen,

and thymus. Toxicology studies demonstrated mild hepatotoxicity in rats fed 2.1 or 7 mg/kg daily for a year (21). Similar dog studies showed no toxicity (21). Fetotoxicity was noted in rats and mice (21).

2.1.2 Human Cysticercosis



Cysticercosis in humans is caused by the larval stage of the cestode *Taenia solium* (pig tapeworm). The normal life cycle of this parasite includes the pig, which acts as an intermediate host with larval vesicles in its tissues, and the human, which is the definitive host, harboring the adult worm in the intestinal tract. The adult worm is relatively harmless; however, humans can also serve as an intermediate host by ingesting *Taenia* eggs and developing the cystic form of the infection in various tissues (24). The cysts, which may be up to several centimeters in diameter, may occur anywhere in the body, including subcutaneous tissue, muscle, eye, and most seriously, in the CNS. Neurocysticercosis, the presence of these cysts in the brain parenchyma, causes a variety of symptoms, the most common of which is seizures (5, 6). Subarachnoidal or intraventricular cysts may also cause intracranial hypertension (25).

2.1.3 Global Significance

Neurocysticercosis is common in developing countries that practice pig husbandry. The disease is endemic throughout Latin America, Indonesia, Africa and parts of India. In Mexico, Ecuador, and Brazil, the prevalence of neurocysticercosis found at autopsy exceeds 1% (26, 27). In Mexico (28) and Peru (29), 12% of acute neurological hospital beds are occupied by patients with neurocysticercosis. Interestingly, epilepsy is more frequent in developing countries than it is in developed countries. In a community survey in Ecuador, the prevalence of epilepsy was 12/1000 (30), and in Peru it was 16.6/1000 (31). These rates are 2-3 times those in industrialized countries (32). It is assumed, based on serological studies in India (33), South Africa (34, 35), Mexico (36), and Peru (2), that the increased rates of epilepsy are due to neurocysticercosis.

In the US, neurocysticercosis is diagnosed relatively commonly in hospitals that treat large Hispanic populations (e.g., hospitals in Los Angeles and San Diego) (37-39). The number of reported cases is increasing, probably as a result of better diagnosis and of increased immigration of *T. solium*-infected individuals. The number of indigenous cases is also rising,

even though pigs are not a source of infection in the US (38-41). A recent cluster of cysticercosis cases in orthodox Jews in Brooklyn, New York, was attributed to tapeworm infections in their Latin American domestic workers (36).

2.1.3.1 Current Therapy

For many years, therapeutic approaches to neurocysticercosis were limited to the use of steroids and surgery for the relief of intracranial hypertension (24). In 1978, praziquantel was recognized as the first antiparasitic drug with activity against neurocysticercosis (42-46). In 1989, albendazole was reported to be effective (47), and it became widely used because of its efficacy and low cost (6, 47-50). Initially, the suggested duration of albendazole therapy was 30 days (47), but shorter schedules of 8 or 15 days were successfully used (51, 52). We have reported the results of a prospective double blind trial, in which a seven-day course of albendazole decreased the number of parasites in 78% of patients, but complete cure was achieved in less than 40% of patients (53). The available therapy is clearly limited by marginal efficacy and the requirement for prolonged treatment (49, 53).

2.1.3.2 Oxfendazole for Porcine Cysticercosis

No suitable single-dose therapy is currently available for porcine cysticercosis. Albendazole is effective when used in a 3-day treatment schedule, but not in a single dose (54). We performed two studies in Peru that suggest that in pigs, a single oral dose of oxfendazole is highly effective against the larval form of *T. solium.* In the first study, naturally parasitized pigs were divided into four groups and treated with single oral doses of oxfendazole (30 mg/kg; 1078 mg/m^2), praziquantel (50 mg/kg), oxfendazole plus praziquantel, or placebo.(9) At necropsy 10-12 weeks later, the psoas and anconeal muscles, tongue, heart, and brain were dissected; cysts were removed, counted, and tested for viability. Importantly, oxfendazole treatment effected a 100% elimination of viable parasites in all four tissues, whereas praziquantel was ineffective. In a second, similarly designed study, the efficacies of single oral doses of 10, 20, or 30 mg/kg (359-1078 mg/m^2) oxfendazole were compared with placebo. All three doses eradicated parasites from the heart; there was a dose-dependent reduction in parasites from muscle (88.7-97.4%); and at all dose levels, there was a substantial reduction (83%) in parasites from brain and tongue,(8) effects that were confirmed in a third study (10). These studies demonstrate that single oral doses of oxfendazole are effective against *T. solium* in pigs, suggesting that in humans, comparable oral doses of 359 mg/m^2 (9.49 mg/kg) oxfendazole might have substantial anti-cysticercosis activity.

2.2 Rationale

With current treatment strategies for neurocysticercosis, cure is achieved in approximately 50% of patients despite multiple doses of drug (1, 5-7). In animal studies, single oral doses of oxfendazole appear to have substantial activity against the tissue stages of (*Taenia solium*) (8-10). Oxfendazole, as a single dose, might be efficacious against neurocysticercosis in

humans. A Phase I study is needed to evaluate its safety, metabolism, and pharmacokinetics (PK) in humans.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

This study is the first time that oxfendazole will be evaluated in humans. However, there are approved antiparasitic agents that have chemical similarities to oxfendazole. A single dose of the approved antiparasitic agent albendazole in humans is largely without side effects. More prolonged courses have been associated with liver abnormalities and bone marrow suppression. It has been associated with headache, gastrointestinal side effects (abdominal pain and nausea) in less than 10 % of subjects as well as rare allergic reactions (rash, urticaria, Stevens-Johnson syndrome) in less than 1 %. We expect that oxfendazole may have similar gastrointestinal events and rare allergic reactions, though this will be the first study in humans.

In animal studies, lower OXF doses and shorter periods of administration similarly result in no observable toxicity. At higher doses, the principal target organs are bone marrow and liver, WBC count rapidly recovers when OXF administration is discontinued. In the present study, only a single dose of oxfendazole will be administered to each subject.

In animal studies, fetotoxicity was reported and changes in the testes were seen.

Subjects will be closely monitored by history, physical examination and laboratory tests to assess safety and tolerability. Subjects will be carefully monitored for AEs and blood studies will be monitored to assess for any changes in the complete blood counts, liver and renal function and coagulation factors. As for any experimental drug, there may be side effects of oxfendazole that are not presently known. EKG studies will be performed to assess for cardiac effects.

This study will not recruit women of child bearing potential. Men will be counseled to use condoms and avoid pregnancy attempts for 4 months following drug administration.

There are no significant side effects from electrocardiogram (EKG) other than cosmetic annoyance from the glue employed to hold the leads. Venipuncture can result in pain or discomfort, and less likely, the possibility of bruising, or infection at the site, or fainting. Loss of confidential health information could occur.

Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the subjects' PHI. All records will be kept in a locked file cabinet or maintained in a locked room at the participating VTEU sites. Electronic files will be password protected. Only people who are involved in the conduct, oversight, monitoring, or auditing of this study will be allowed access to the PHI that is collected. Any publications from this study will not use information that will identify subjects by name. Organizations that may inspect

and/or copy research records maintained at the participating VTEU sites for quality assurance and data analysis include groups such as: National Institute of Allergy and Infectious Diseases (NIAID) and Food and Drug Administration (FDA). There may be other unknown side effects.

2.3.2 Known Potential Benefits

There will be no direct benefit to subjects.

3 OBJECTIVES

3.1 Study Objectives

Primary:

- Assess the safety and tolerability of oxfendazole in healthy adults.

Secondary:

- Assess the pharmacokinetic profile of oxfendazole
- Assess the metabolism of oxfendazole

3.2 Study Outcome Measures

3.2.1 Primary endpoint:

3.2.1.1 The rate of adverse events (AEs) related to oxfendazole within 14 days of receipt of a single oral dose.

3.2.2 Secondary endpoints:

3.2.2.1 Plasma Cmax, Tmax, AUC, t1/2 of oxfendazole for each dosage group.

3.2.2.2 Plasma and urine concentrations of oxfendazole fenbendazole and oxfendazole sulfone at time points specified in Appendix A Schedule of Events and described in Section 4 Study Design relative to oral dosing.

4 STUDY DESIGN

This Phase I study is a randomized, double-blind, placebo-controlled evaluation of the safety and PK of escalating single oral doses of oxfendazole (0.5, 1, 3, 7.5, 15, 30, 60 mg/kg) in healthy volunteers. The dose will be increased approximately three-fold (one-half log) at each increment, and each cohort will comprise 10 volunteers (8 drug, 2 placebo). Subjects will be monitored for 2 weeks after dosing, including monitoring the PK and metabolism of oxfendazole in blood and urine.

Two sentinel subjects (one randomized to receive study drug and the other to receive placebo) will be dosed and monitored 48 hours for adverse events prior to enrolling the remaining subjects in each cohort. If no drug-related serious adverse event or laboratory grade 3 study drug related events are observed within the 48 hour period, the remainder of the cohort will proceed with dosing. Each new cohort will be dosed only after the 2-week safety data for the preceding group have been analyzed. A Safety Review Committee (SRC) composed of the Protocol Principal Investigator and Independent Safety Monitor will review blinded safety data for the completed cohort. If a clinically significant AE is observed that is possibly drug related, the SRC will determine if an ad hoc SMC meeting should be called. Up to 70 volunteers (56 drug, 14 placebo) will complete the study. The Safety Monitoring Committee (SMC) will review the safety data either when or if the final dose is reached.

For the Phase I study, between 10 and 70 subjects (8:2 drug: placebo in each cohort receiving increasing doses) will be enrolled. This number should be small enough to perform the study safely and efficiently, yet large enough for an estimation of the PK, metabolism, and the identification of any common side effects of oxfendazole.

The study will be conducted on an outpatient basis at the University of Iowa. Screening for subject recruitment will continue throughout the study until the requisite number of volunteers is enrolled. Each subject will be evaluated over a 2 week period. Projected duration of subject participation will be 3-6 weeks of face to face visits, including the screening period. It is anticipated that it will take 18 months to finish the study.

During the screening process written informed consent will be obtained prior to any study activities. A complete medical history will be obtained including review of medications, supplements and vitamins. Vital signs including oral temperature, blood pressure, pulse, height, weight and an EKG will be performed and a routine physical exam will be performed by a licensed clinician. Laboratory tests for hemoglobin, white blood cell count with neutrophil and eosinophil count, platelet count, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, random glucose, urine dipstick for protein and glucose, hepatitis B surface antigen, hepatitis C antibody, and human immunodeficiency virus serology (HIV) will be conducted. Eligible subjects will be invited to join the study. They will be advised to

abstain from drug or alcohol use for the 48 hours prior to return on Day 1 and to avoid tobacco use from the day of screening through the end of the study.

On study Day 1, a review of the inclusion/exclusion criteria will be conducted with subjects. A brief interim medical history will be taken and review of medication history since screening visit. Vital signs, including oral temperature, blood pressure, and pulse will be obtained. A targeted physical exam will be performed by a licensed clinician. Blood will be drawn for baseline PK and safety laboratory tests (hemoglobin, white blood cell count with neutrophil and eosinophil count, platelet count, creatinine, Na, K, Cl, CO2, urea nitrogen, alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time and partial thromboplastin time, total bilirubin, and urine dipstick for protein and glucose) and a spot urine sample will be obtained for PK baseline.

Volunteers will be randomized using the EMMES web-based application to receive a single oral dose of oxfendazole or placebo. The designated unblinded pharmacist will prepare the study product according to the treatment assignment for each subject.

Subjects will be administered a single oral dose of coded oxfendazole/placebo by a blinded study nurse or investigator. Subjects will be fasting for 8 hours prior to, and for two hours after, the administration of drug/placebo. On day of drug administration, lunch and dinner will be provided. Monitoring will start immediately after dosing and will continue for 2 weeks.

On Day 1, subjects will be interviewed briefly to monitor for AEs and SAEs. Blood for oxfendazole and metabolites will be drawn at 0 (product administration), 1, 2, 4, 6, 8, 10, and 12 hours. Urine for oxfendazole and metabolites will be collected for 0-4, 4-8, 8-12, and subjects will be sent home with a 24 hour urine container to collect all urine between 12-24 hours. After 12 hours, the subjects will be allowed to return home. Subjects will be counseled to avoid drug, alcohol and tobacco use through the end of the study (day 15).

On Day 2, subjects will be interviewed briefly to review for concomitant medications, and any AEs or SAEs since the last visit. Vital signs, including oral temperature, blood pressure, and pulse will be obtained. A targeted physical exam will be performed if indicated by symptoms. Blood for oxfendazole and metabolites will be collected between 24-32 hours, and urine for oxfendazole and metabolites will be collected for the time frame 12–24 hours. A urine creatinine value will be tested on the 12-24 hours sample and used to calculate creatinine clearance.

On Day 3, subjects will be interviewed briefly to review for concomitant medications, and any AEs or SAEs since the last visit. Vital signs, including oral temperature, blood pressure, and pulse will be obtained. A targeted physical exam will be performed if indicated by symptoms. Blood for oxfendazole and metabolites will be collected at a time point between 48-60 hours, and a spot urine for oxfendazole and metabolites will be collected between 48-60 hours. Blood for safety laboratories (hemoglobin, white blood cell count with neutrophil and eosinophil count, platelet count, creatinine, Na, K, Cl, CO2, urea nitrogen, alanine aminotransferase (ALT),

aspartate aminotransferase (AST), prothrombin time and partial thromboplastin time, total bilirubin) will be obtained for the two sentinel subjects only.

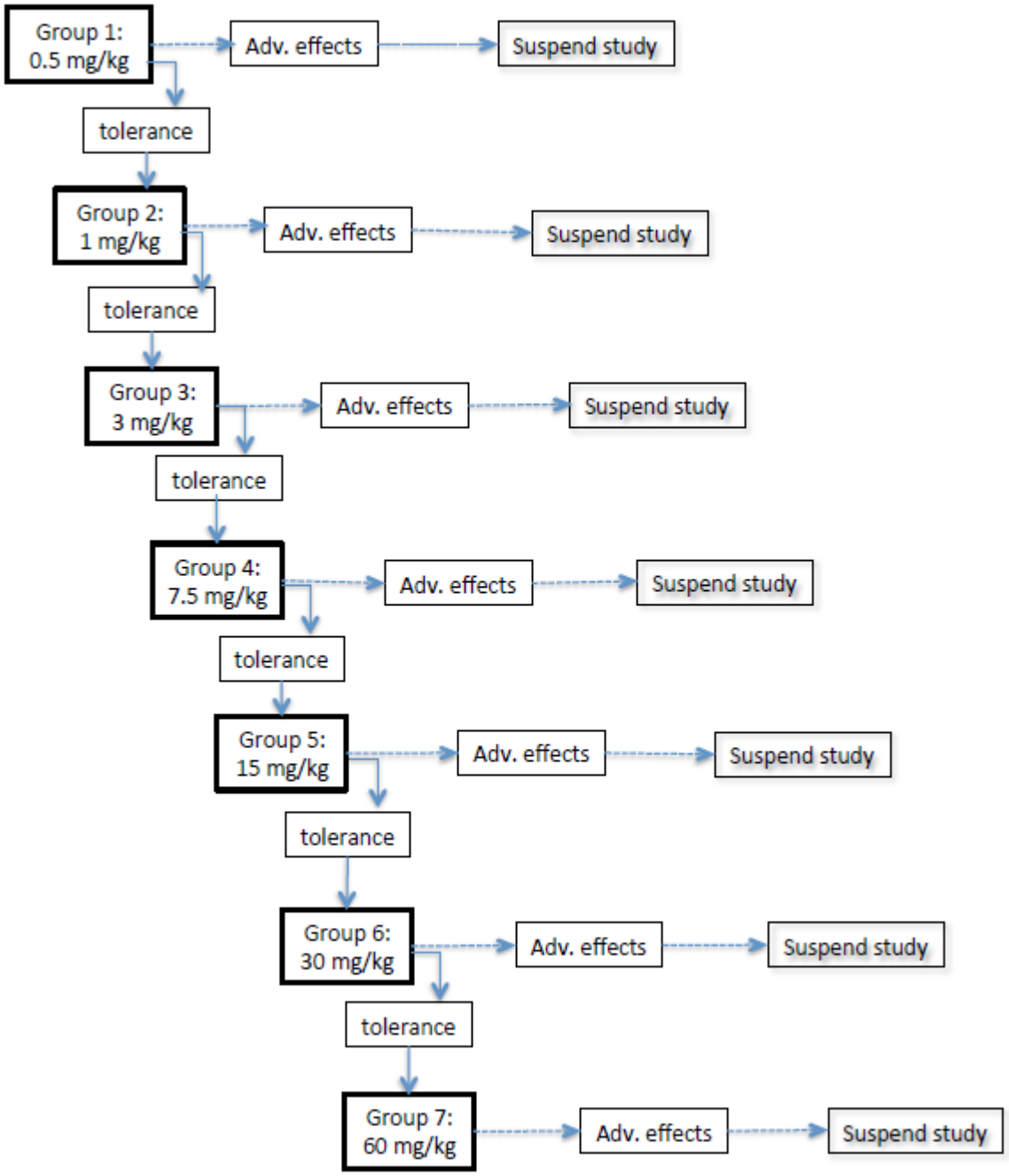
On Day 4, subjects will be interviewed briefly to review for concomitant medications, and any AEs or SAEs since the last visit. Vital signs, including oral temperature, blood pressure, and pulse will be obtained. A targeted physical exam will be performed if indicated by symptoms. Blood and urine will be obtained for PK and safety studies (hemoglobin, white blood cell count with neutrophil and eosinophil count, platelet count, creatinine, Na, K, Cl, CO2, urea nitrogen, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, prothrombin time and partial thromboplastin time, , and urine dipstick for protein and glucose). An EKG will be performed.

On Day 6, subjects will be interviewed briefly to review for concomitant medications, and any AEs, or SAEs since the last visit. Vital signs, including oral temperature, blood pressure, and pulse will be obtained. A targeted physical exam will be performed if indicated by symptoms. Blood for oxfendazole and metabolites will be collected.

On Days 8 and 15, subjects will be interviewed briefly to review for concomitant medications, and any AEs, or SAEs since the last visit. Vital signs, including oral temperature, blood pressure, and pulse will be obtained. A targeted physical exam will be performed if indicated by symptoms. Blood for oxfendazole and metabolites as well as safety panels (hemoglobin, white blood cell count with neutrophil and eosinophil count, platelet count, creatinine, Na, K, Cl, CO2, urea nitrogen, alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time and partial thromboplastin time, total bilirubin, and urine dipstick for protein and glucose) will be collected.

Clinical laboratory evaluations will be performed by the University of Iowa Clinical Pathology Laboratory. Samples for PK studies will be processed at Dr. Daryl Murry's laboratory at the University of Iowa. The primary outcome measure in this study is: The rate of adverse events (AEs) related to oxfendazole within 14 days of receipt of a single oral dose.

Note: Two sentinel subjects will receive the study product (1 drug/ 1 placebo) dose in each group and monitored 48 hours for adverse events prior to completing enrollment of the remaining 8 subjects in the group. Adverse events assessed as related to the study product and as defined in the Halting Rules may result in suspension of the study.



Safety oversight per DMID guidelines will be provided by an independent Safety Monitoring Committee (SMC) (Refer to http://www.niaid.nih.gov/dmid/clinresearch/). The committee will be

composed of individuals who are not directly involved in the study. A local independent safety monitor (ISM) from the University of Iowa who will provide local medical consultation for the study, but will not serve as a voting member of the SMC. The committee will meet to review cumulative safety data, adherence to the protocol and data relevant to proceeding. (Refer to **Section 9.6**)

Study Enrollment and Withdrawal
Up to 70 males and females (non-childbearing potential), 18-45 years old, inclusive, who are in good health and meet all eligibility criteria, will be enrolled at the University of Iowa. Estimated time to complete enrollment in this study is 17 months.

The target population will reflect the community at large in the Iowa City area. Volunteers will be sought from the University of Iowa VTEU registry of previous participants, web announcements and other mechanisms. Information regarding the study may be provided to the subjects who have previously participated in trials conducted at the participating VTEU sites. Other forms and/or mechanisms of recruitment may also be used.

The University of Iowa IRB will approve all methods of recruitment and recruitment materials prior to use.

The initial responders will be screened by telephone to eliminate those who do not meet inclusion criteria or who have exclusion criteria. Successful candidates will be asked to come to the clinic to further assess their eligibility.

Subject Inclusion and Exclusion Criteria must be assessed by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

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

4.1 Subject Inclusion Criteria

It is the intent of this study to enroll subjects who are considered healthy volunteers. Subjects with pre-existing clinically significant conditions are not considered normal, healthy volunteers. Inclusion criteria must be assessed by a clinician licensed to make medical diagnoses. Subjects must meet all of the following inclusion criteria to participate in this study:

1. Males and females of non-childbearing potential between the ages of 18 and 45 years, inclusive.*

   *Surgically sterile via tubal ligation, bilateral oophorectomy or hysterectomy or who have been postmenopausal for ≥1 year confirmed by LH and FSH levels.

2. In good health, as judged by the investigator and determined by vital signs*

   *Temperature < 38°C, heart rate ≤ 100 bpm and > 50 bpm, systolic blood pressure ≤ 140 mmHg and > 89 mmHg, diastolic blood pressure ≤ 90 mmHg and ≥ 60 mm Hg, medical history and a targeted physical examination. BMI ≥18 and ≤ 35. Athletically trained subjects with a pulse ≥ 45 may be enrolled at the discretion of the principal investigator or designated licensed clinical investigator.

3. Acceptable screening laboratories*

   *Hemoglobin, white blood cell (WBC) count, neutrophil, eosinophil and platelet counts within normal ranges. AST < 44 and ALT < 44 and total bilirubin, creatinine must be equal to or below the upper limit of normal (for eosinophil count, AST, ALT, creatinine, and total bilirubin values below the normal range are acceptable). Random blood glucose must be <140. Urine dipstick testing must be negative for glucose and negative or trace for protein. The following serology tests must be negative: HIV 1/2 antibody, hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV) antibody. HIV and hepatitis C viral load PCR testing may be performed for individuals suspected of having indeterminate antibody testing.

4. Male participants must be willing to ensure use of condoms and spermicides for 4 months after study drug administration.
5. Provide written informed consent before initiation of any study procedures.
6. Willing to be available for all study-required procedures, and visits for the duration of the study.
7. Able to provide a home phone number, and the name, address, and/or email of a person willing to assist with making contact during the follow-up phase of the study.

4.2 Subject Exclusion Criteria

Subjects who meet any of the exclusion criteria at Screening/Baseline will be excluded from study participation. Exclusion criteria must be assessed by a clinician licensed to make medical diagnoses. Subjects will not be able to participate if they have any of the following:

1. History of residing for 6 or more months in regions with endemic cysticercosis as determined by the principal investigator or a designated study physician.
2. Breastfeeding females.
3. Body temperature ≥100.4°F (≥38.0°C) or acute illness within 3 days before administration of study drug (subject may be rescheduled).
4. Chronic or acute medical disorder*

   *Disorders of the cardiac, pulmonary, liver, kidney, neurologic, gastrointestinal or other system, such that in the opinion of the investigator participation in the study creates additional risk to the subject, or to the validity of the study.

5. Use of chronic systemic medications*

   *Intermittent use of over the counter medications such as acetaminophen, ibuprofen, cold and sinus medications are permitted for enrollment (please see section 5.6 for instructions on medication use during the study). Topical medications, nasal steroids are permitted throughout the study. Use of prescription medications used less than once per week on average are permitted for enrollment (see section 5.6 for instructions on medication use

during the study). If the subject has taken a short term prescription medication within the past 30 days (e.g. an antibiotic), they should be postponed from enrollment until 30 days have elapsed since the last dose.

6. Has history of sensitivity to related benzimidazole compounds (e.g., albendazole, mebendazole).
7. A diagnosis of schizophrenia, bipolar disease, or history of hospitalization for a psychiatric condition or previous suicide attempt.
8. A history of treatment for any other psychiatric disorder in the past 3 years.*

   *Past treatment for ADHD does not exclude participants from enrollment as long as the medications have been discontinued for a minimum of 3 months and symptoms are well controlled.
9. Received an experimental agent* within 1 month before administration of study drug or expect to receive an experimental agent during the 15-day study period.

   *Vaccine, drug, biologic, device, blood product, or medication.
10. Any condition that would, in the opinion of the investigator, place them at an unacceptable risk of injury, render them unable to meet the requirements of the protocol, or that may interfere with successful completion of the study.
11. A history of alcohol consumption* or any illicit drug use[†], or history of substance abuse[#]. Individuals must agree to abstain from drug or alcohol use for 48 hours prior to enrollment through day 15. .

    *Greater than 7 alcoholic drinks per week. .

    [†]Other than occasional marijuana use (less than once per week for the past 60 days is acceptable).

    [#]Alcohol or illicit drugs within the past 3 years.
12. History of chronic tobacco use in the past 60 days.*

    *A history of occasional tobacco use (less than 1 pack per week on average) is acceptable. Individuals will be counseled to abstain from use of tobacco and marijuana from screening through day 15.

Vital signs may be performed up to three times to allow for transient conditions to resolve. Screening laboratory values that are abnormal, but are considered to be abnormal due to an acute illness or process may be repeated once. Creatinine, AST, ALT, bilirubin and eosinophil count values that fall below normal values specified in the DMID Toxicity Table are not considered abnormal for the purposes of this study. Additionally, abnormalities in the RBC parameters other than hemoglobin and abnormalities in the WBC differential not specified in the inclusion criteria above (e.g. low basophils or eosinophils) will not be considered exclusionary

for this study and will be followed with the standard safety laboratory follow-up outlined in the study. Laboratory values that are performed as a standard panel by the clinical laboratory, but are not requested for the study, will be reviewed by a licensed study clinician and the clinician will determine whether the laboratory abnormality is clinically significant and should be considered exclusionary. If determined to be clinically insignificant, the study team is not required to follow the laboratory until resolution or the value is determined to be clinically stable.

4.3 Treatment Assignment Procedures

4.3.1 Randomization Procedures

Randomized treatment assignments will be generated by a statistician at The EMMES Corporation, the statistical and data coordinating center (SDCC) for this study. Subjects will be registered using a web-based application developed by The EMMES Corporation. Upon entry of demographic data and confirmation of eligibility for the trial, the subject will be enrolled. After successful enrollment, a treatment assignment number will be displayed on the Enrollment Confirmation screen. The treatment assignment number is referenced against a confidential randomization list provided to designated study personnel on-site to determine the study assignment. The EMMES Corporation will monitor the implementation of this process. Two sentinel subjects in each cohort, one receiving study drug and one receiving placebo, will be dosed and monitored for safety for 48 hours prior to enrolling the remainder of the cohort. As further randomization in the group occurs, these two subjects will be incorporated into the subsequent randomization scheme.

4.3.2 Masking Procedures

This is a double-blinded, placebo controlled trial. Aliquots of 22.5% or 9.6% Synanthic® suspension or placebo solution will be prepared by an unblinded clinical research pharmacist (See Section 6.2, Table 3) and administered orally by a blinded study nurse or investigator using an oral dosing syringe. Immediately following administration of the dose, the subject will drink 100 mL of water to ensure that the entire dose is taken.

4.3.3 Reasons for Withdrawal

Subjects may voluntarily withdraw their consent for study participation at any time and for any reason, without penalty.

Any enrolled subject may withdraw or be withdrawn from the study for the following reasons:

- 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.

- Subject no longer meets eligibility criteria.
- As deemed necessary by the site principal investigator or appropriate sub-investigator for noncompliance or other reasons.
- Subject withdrawal of consent.
- Subject lost to follow-up.
- Termination of the study.
- New information becomes available that makes further participation unsafe.

If a subject withdraws or is withdrawn prior to completion of the study, the reason for this decision must be recorded in the case report forms (CRFs). Refer to Section 7.5 for procedures to be followed if a subject withdraws from the study.

4.3.4 Handling of Withdrawals

The primary reason for withdrawal from the study will be recorded on the Study Status data collection form. Subjects will be encouraged to complete the Early Termination Visit. The Early Termination Visit procedures are listed in Section 7.5. Although subjects are free to withdraw at any time or may be withdrawn by the site principal investigator or appropriate sub-investigator at any time, subjects who receive study drug will be encouraged to remain in the study for follow-up safety assessments and collection of venous blood samples for safety testing. Every attempt will be made to follow all adverse events, including systemic reactions, serious adverse events, ongoing at the time of early withdrawal to resolution.

In the case of subjects who fail to appear for a follow-up safety assessment, extensive effort (i.e., three documented contact attempts via phone calls, e-mails, etc., made on separate occasions and followed by a certified letter) will be made to locate or recall them, or at least to determine their health status. These efforts will be documented in the subject’s records.

Subjects who withdraw, or are withdrawn or terminated from the study, or are lost to follow-up after signing the informed consent form, randomization, and receipt of study drug will not be replaced. Unless prohibited by the volunteer, data and samples obtained prior to withdrawal will be included in study analysis. Subjects who withdraw, or are withdrawn or terminated from the study, or are lost to follow-up after signing the informed consent form and randomization but before receipt of study product may be replaced.

4.3.5 Termination of Study

The NIAID/DMID has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- Incidence or severity of AEs indicating a potential health hazard
- Data recording is inaccurate or incomplete
- The Investigator has not been adhering to the protocol or applicable regulatory guidelines in conducting the study

5 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

5.1 Study Product Description

5.1.1 Acquisition

Oxfendazole suspension will be purchased through a commercial supplier of the over the counter product.

Oxfendazole placebo solution will be obtained from SRI International. The product was manufactured under cGMP conditions.

5.1.2 Formulation, Packaging, and Labeling

Oxfendazole suspension is currently available as a 9.06% and a 22.5% suspension. Both strengths will be used in this study, as specified in Table 3 (Section 6.2). Dose levels of 0.5, 1, 3, 7.5, 15, 30, and 60 mg/kg will be evaluated sequentially, the dose increasing with each new cohort. Doses will be administered orally using a syringe of a size appropriate to measure the needed volume. A placebo will be prepared by SRI and will also be administered with an oral dosing syringe.

The oxfendazole placebo formulation consists of polyethylene glycol, methyl paraben, and sterile water for injection. These excipients, widely used in pharmaceutical formulations, are NF (National Formulary) or USP (United States Pharmacopeia) grade listed in the FDA's inactive ingredient list. The 15 mL of oxfendazole placebo solution is filled into pre-cleaned 22 mL screw thread vial with 20/400 PTFE (polytetrafluoroethylene) lined cap. Table 2 describes the amount of each excipient in the formulation, container, and closure of oxfendazole placebo.

Table 2: Oxfendazole Placebo Formulation and Packaging

Item	Material	Amount % (w/v)
1	Polyethylene Glycol, NF	4.5%
2	Methyl Paraben, NF	0.18%
3	Sterile Water For Injection, USP	95.32%
4	22 mL Screw Thread Vial with 20/400 PTFE Lined Cap	N/A
Total		100.00

Corrugated box inserted with vials partition will be used to pack oxfendazole placebo vials.

Each vial has been affixed with a 2" x 4" open text label. The label text is described in Figure 1.

Figure 1: Oxfendazole placebo label text description

Oxfendazole Placebo, 15 mL

Batch No.: 16146-10 Manufacture Date: Oct. 2013

Store at temperature not exceeding 25°C (77°F)

Caution: New Drug Limited by Federal (US) Law to Investigational Use Only. Keep out of the reach of children.

Manufactured for the National Institute of Allergy and Infectious Disease (NIAID), Bethesda, MD 20817
by SRI International, Menlo Park, CA 94025

5.1.3 Product Storage and Stability

Oxfendazole should be stored at room temperature (20º- 25º C) though excursions between 15º and 30ºC for less than 24 hours are acceptable.

Oxfendazole placebo is recommended to store at temperatures not to exceed 77°F (25°C).

The stability of oxfendazole placebo is under evaluation. The stability study at 25°C/60% RH (testing at 3, 6, 9 and 12 months) and 40 °C/75% RH (testing at 3 and 6 months) has been initiated.

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

Table 3. Schema for administration of Synanthic® available product strengths

Dose ID	Synanthic®		Dosing protocol		
	Concentration of dosing suspension (mg/mL)	Source of dosing suspension	Protocol dose (mg/kg)	mL to be administered	Vol for 80 kg subject (mL)
A	90.6	9.06% Synanthic®	0.5	kg x 0.0055	0.44
B			1.0	kg x 0.011	0.88
C			3.0	kg x 0.033	2.65
D			7.5	kg x 0.083	6.62
E	225	22.5% Synanthic®	15	kg x 0.067	5.32
F			30	kg x 0.133	10.66
G			60	kg x 0.267	21.33

Note: Aliquots will be removed from the Synanthic® stock bottle immediately after mixing, as the marketed drug is a suspension. The content of the oral dosing syringe will be mixed in the pharmacy and transported to the clinical research for administration. Administration must occur within 20 minutes after mixing in the pharmacy. Immediately following administration of the dose, the subject will drink 100 mL of water to assure that the entire dose is taken. If the dose is not administered within 20 minutes it should be discarded and a fresh dose mixed in the pharmacy.

5.3 Modification of Study Intervention/Investigational Product for a Subject

None as subjects will only receive a single dose.

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

The investigator will sign that he has received the study medication, confirming the quantity received and registering its characteristics, including lot number and expiration date. Upon arrival, the drug will be stored locked in the facilities of each study center at appropriate temperature. The Study Pharmacist (as delegated by the Principal Investigator) will be responsible for appropriate handling and storage of the study medication and ensuring that it is dispensed to study subjects only in accordance with the protocol. A new bottle of Synanthic® will be opened for use on each day of drug administration. A record will be maintained of all study medication dispensed to each subject. Drug suspension not used will be retained in the original containers.

The study products will be sent to the DMID central repository as directed by DHHS, and then will be supplied by the DMID central repository to the participating VTEU site prior to the start of the study.

After receipt of study products, the site principal investigator is responsible for their distribution and disposition, and has ultimate responsibility for study product accountability. Logs of receipt, temperature, maintenance, and disposal must be maintained in the study file. The study product accountability records and dispensing logs will also capture time of preparation of the diluted study drug. IDS staff will develop a master Compounding Record for each product to be prepared and will follow the Departmental SOP for Compounding Procedures during the product preparation.
Each item and volume/weight used in the preparation is double checked. At least one person involved in the process must be a pharmacist. All doses of study drug whether administered or not must be documented on the appropriate study product accountability record or dispensing

log. The sponsor's monitoring staff will verify the participating VTEU sites' study product accountability records and dispensing logs per the site monitoring plan.

Unused bottles of the study products will be retained until monitored and released for disposition as applicable. Final disposition of the unused study drug will be determined by DMID and communicated to the participating VTEU sites by the DMID Clinical Project Manager.

5.5 Assessment of Subject Compliance with Study Intervention/Investigational Product

Oral intake of the study product by the subject will be observed by study personnel. Immediately following administration of the dose, the subject will drink 100 mL of water to assure the entire dose is taken. If vomiting occurs at any time following ingestion of the study product, no further dosing will be provided and subject will continue to be followed for safety and pharmacokinetic analyses. Subjects who have vomiting after administration of the dose will not be replaced.

5.6 Concomitant Medications/Treatments

It is the goal of this study to enroll subjects who are healthy and on no chronic medications. Subjects will be counseled to refrain from taking prescription medications other than topical agents during the study period unless provided by an investigator or other licensed medical provider. Additionally, subjects will be counseled to avoid all over the counter medications unless absolutely necessary and will be asked to consult with a study investigator prior to use of over the counter medications. Subjects will be counseled to avoid acetaminophen since this medication can be associated with hepatotoxicity.

Administration of any medications, therapies, or vaccines will be recorded on the appropriate data collection form. Concomitant medications will include all current medications and medications taken within 30 days prior to signing the informed consent form through Day 15.. Prescription and over-the-counter drugs will be included as well as vitamins and supplements.

Use of new medication should prompt evaluation for the presence of a new diagnosis of chronic medical disease or chronic medical condition.

6 STUDY SCHEDULE (SEE APPENDIX A)

6.1 Screening (Day -28 to -1): Clinic Visit 01

Informed Consent. Written informed consent will be obtained prior to any other study procedures.

History. A complete medical history will be taken by a study nurse or study investigator. Emphasis will be placed on the absence of significant medical or psychiatric illness and the absence of recent illness and recent or current medication, except use of over the counter or prescription medications that are taken on average less than once per week.

Physical Examination.

- A routine physical examination will be performed by a study clinician licensed to make medical diagnoses.
- Height, weight, vital signs including oral temperature, blood pressure, and pulse will be obtained.

Obtain 15 mL of blood for the following studies:

- **Hematology:** Hemoglobin, white blood cell count with neutrophil and eosinophil counts, platelet count.
- **Chemistry**: Creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), random glucose and total bilirubin will be used as screening tests.
- **Serology**: Hepatitis B surface antigen, hepatitis C antibody, human immunodeficiency virus (HIV). If the subject tests positive for HIV or Hepatitis, they will be referred for medical follow-up and counseling.)

Obtain urine sample for:

- **Urine analysis**: Urine dipstick for protein and glucose

EKG. Perform electrocardiogram. EKG will be reviewed by a cardiologist.

Subjects that qualify for enrollment will be asked to agree to the following requirements prior to receipt of the study product:

- Abstain from taking medications, recreational drugs or engaging in alcohol intake 48 hours prior to receipt of the study product and through Day 15.
- Abstain from tobacco use from the time of screening through Day 15.
- Fasting 8 or more hours prior to receipt of study product.

6.2 Enrollment/Baseline (Day 1): Clinic Visit 02

Eligible subjects will be asked to return to the Clinical Research Unit (CRU) having fasted for 8 or more hours.

General.

- Review inclusion/exclusion criteria (including assessment of time of last oral food intake).
- Absence of medications in the past 48 hours will be confirmed.
- A brief interim medical history will be taken.
- A routine physical examination that assesses general appearance and the following areas/systems, including skin, lymph nodes, HEENT, neck, respiratory, cardiovascular, pulmonary, abdomen, extremities, musculoskeletal, and neurological will be performed by a clinician licensed to make diagnoses.
- Vital signs including oral temperature, blood pressure, and pulse will be obtained.
- A heparin lock will be inserted, blood will be drawn (10 mL) for baseline PK and (15 mL) for safety labs (hemoglobin, white blood cell count, including neutrophil and eosinophil counts, platelet count, prothrombin time, partial thromboplastin time, creatinine, Na, K, CL, CO2, urea nitrogen, ALT, AST, total bilirubin).
- Collect urine sample for urine dipstick for protein and glucose and PK baseline.
- **Randomization.** Randomized treatment assignments will be generated by a statistician at The EMMES Corporation, the statistical and data coordinating center (SDCC) for this study. Subjects will be registered using a web-based application developed by The EMMES Corporation. Upon entry of demographic data and confirmation of eligibility for the trial, the subject will be enrolled. After successful enrollment, a treatment assignment number will be displayed on the Enrollment Confirmation screen. The treatment assignment number is referenced against a confidential randomization list provided to the designated unblinded study personnel on-site to determine the study assignment. The EMMES Corporation will monitor the implementation of this process.

Administration of Study Medication (drug/placebo).

A blinded study nurse will administer a single oral dose of coded oxfendazole/placebo to the subject. Escalating dose levels of 0.5, 1, 3, 7.5, 15, 30, and 60 mg/kg will be evaluated sequentially.

- Subjects will remain fasting for two hours after the administration of drug/placebo.
- Lunch and dinner will be provided. Subjects will be allowed to eat snacks but will be asked to avoid drinking grapefruit juice and excessive (>2 cups) coffee.
- 10 mL of blood for oxfendazole and metabolites will be drawn at at baseline (prior to product administration), 1, 2, 4, 6, 8, 10, and 12 hours (all times have a window of +/- 15 minutes except the 10 and 12 hour samples which have a window of +- 30 minutes- it is critical to record the exact time of blood draw).

- Urine will be collected (prior to product administration) and for the first 24 hours following drug administration. Following drug administration, urine for oxfendazole, metabolites will be collected for 0-4, 4-8, 8-12, and subjects will be sent home with a 24 hour urine container to collect all urine between 12-24 hours. A urine creatinine value will be tested on the 12-24 hours sample and used to calculate creatinine clearance.
- Assess adverse events throughout the day and prior to discharge from the CRU.
- Assess for AEs and SAEs
- Counsel on need to avoid alcohol, drugs, tobacco and medications throughout the study.

6.3 Follow-up (Days 2 – 8): Visits 03 through 07

Clinic Visit 03, Day 2

- Vital signs including oral temperature, blood pressure, and pulse will be obtained.
- A targeted physical exam may be performed, if indicated.
- Review concomitant medications
- Review for AEs and SAEs
- Counsel on need to avoid alcohol, drugs, tobacco and medications throughout the study.
- 10 mL of blood for oxfendazole and metabolites will be drawn at 24 (+ 8) hours.
- Spot urine for oxfendazole, metabolites will be collected at 24 (+8) hours.

Clinic Visit 04, Day 3

- Vital signs including oral temperature, blood pressure, and pulse will be obtained.
- A targeted physical exam may be performed, if indicated.
- Review concomitant medications
- Review for AEs and SAEs
- Counsel on need to avoid alcohol, drugs, tobacco and medications throughout the study.
- Collect 10 mL of blood for oxfendazole and metabolites.
- For the two sentinel subject only, collect 15 mL of blood for safety laboratory analysis (hemoglobin, white blood cell count with neutrophil and eosinophil count, platelet count, creatinine, Na, K, Cl, CO2, urea nitrogen, alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time and partial thromboplastin time, total bilirubin).
- Spot urine for oxfendazole, metabolites will be collected between 48-60 hours.

Clinic Visit 05, Day 4

- Vital signs including oral temperature, blood pressure, and pulse will be obtained.
- A targeted physical exam may be performed, if indicated.
- Review concomitant medications
- Review for AEs and SAEs
- Counsel on need to avoid alcohol, drugs, tobacco and medications throughout the study.
- Collect 10 mL of blood for oxfendazole and metabolites.

- Collect 15 mL of blood for safety panels (hemoglobin, white blood cell count, including neutrophil and eosinophil counts, platelet count, prothrombin time, partial thromboplastin time, Na, K, Cl, CO2, urea nitrogen, creatinine, ALT, AST, total bilirubin, urine dipstick for protein and glucose) will be collected.
- An EKG will be performed. EKG will be reviewed by a cardiologist.

Clinic Visit 06, Day 6 (+/- 1 day):

- Vital signs including oral temperature, blood pressure, and pulse will be obtained.
- A targeted physical exam may be performed, if indicated.
- Review concomitant medications
- Review for AEs and SAEs
- Counsel on need to avoid alcohol, drugs, tobacco and medications throughout the study.
- Collect 10 mL of blood for oxfendazole and metabolites.

Clinic Visit 07, Day 8 (+/-1 day):

- Vital signs including oral temperature, blood pressure, and pulse will be obtained.
- A targeted physical exam may be performed, if indicated.
- Review concomitant medications
- Review for AEs and SAEs
- Counsel on need to avoid alcohol, drugs, tobacco and medications throughout the study.
- Collect 10 mL of blood for oxfendazole and metabolites.
- Collect 15 mL of blood for safety panels (hemoglobin, white blood cell count, including neutrophil and eosinophil counts, platelet count, prothrombin time, partial thromboplastin time, Na, K, Cl, CO2, urea nitrogen, creatinine, ALT, AST, total bilirubin, urine for dipstick testing for protein and glucose) will be collected.
- An EKG will be performed and will be reviewed by a cardiologist.

6.4 Final Study Visit, Clinic Visit 08 (Day 15) (+/-2 days):

- Vital signs including oral temperature, blood pressure, and pulse will be obtained.
- A targeted physical exam may be performed, if indicated.
- Review concomitant medications
- Review for AEs and SAEs
- Collect 10 mL of blood for oxfendazole and metabolites.
- Collect 15 mL of blood for safety panels (hemoglobin, white blood cell count, including neutrophil and eosinophil counts, platelet count, prothrombin time, partial thromboplastin time, Na, K, Cl, CO2, urea nitrogen, creatinine, ALT, AST, total bilirubin, urine for dipstick testing for protein and glucose) will be collected.
- An EKG will be performed and will be reviewed by a cardiologist.

6.5 Early Termination Visit

If a subject withdraws from the study early, the following procedures should be performed at the early termination visit.

- Review current health status (interim medical history) and note any changes since the last visit
- Review concomitant medications
- Blood will be collected for safety laboratory tests
- If early termination is prior to 72 hours after administration of the drug, urine will be obtained for PK studies
- A targeted physical examination may be performed, if indicated.
- Information regarding AEs and SAEs will be solicited. Any ongoing AEs or SAEs will be followed to resolution or until a stable chronic condition has been established.

Follow-up assessments will be completed according to the protocol schedule, if possible.

6.6 Unscheduled Visit

Unscheduled visits may occur at any time during the study. Unscheduled visits may occur after the scheduled final study visit (Day 15) if necessary to follow any AE occurring during the study period to resolution or stability. The procedures below are to be performed at any unscheduled visit. See the Manual of Procedures (MOP) for instructions on documentation and data reporting.

- Interim medical history will be reviewed.
- Review concomitant medications.
- Vital signs (P, BP, oral T), if clinically indicated will be obtained.
- A targeted physical exam, if indicated based on symptoms will be performed.
- Adverse events and serious adverse events will be reviewed.

6.7 Handling of Abnormal Liver Function or Hematological Tests

Preclinical tests demonstrated changes in liver function and hematological tests. Subjects demonstrating a grade 3 or higher change in hematological parameters of absolute neutrophil count, hemoglobin, or platelet count or ALT or AST greater than 3 times the upper limit of normal or total bilirubin greater than 2 x the upper limit of normal will be asked to return for repeat testing within 72 hours of detection of the abnormal laboratory test. Repeat testing of any change in the complete blood count or absolute neutrophil count will require a repeat CBC with differential. Any change in the mentioned liver function tests (ALT, AST, or total bilirubin) will require repeat evaluation of all 4 liver tests. Testing should be repeated 2-3x per week until the laboratory value stabilizes or has returned to normal. All of the evaluations listed under “unscheduled visits” will apply for these return visits that require additional laboratory testing.

7 STUDY PROCEDURES/EVALUATIONS

7.1 Clinical Evaluations

Medical History: Will be obtained by interview of the subjects. Subjects will be queried regarding a history of significant medical disorders of the head, eyes, ears, nose, throat, mouth, cardiovascular system, lungs, gastrointestinal tract, liver, pancreas, kidney, nervous system, blood, lymph glands, endocrine system, musculoskeletal system, skin, and genital/reproductive tract. A history of any allergies, cancer, immunodeficiency, psychiatric illness, substance abuse, and autoimmune disease will be solicited.

Concomitant Medications: All current medications and medications taken in the 30 days before enrollment (prescription and over-the-counter drugs) will be documented, as well as vitamins and supplements, through 14 days after receipt of study product. Assessment of eligibility also will include a review of prohibited medications (per the exclusion criteria).

Physical Examination: This examination will be conducted at Screening and Visit 2 and will assess general appearance including height and weight (at Screening only), vital signs (blood pressure, temperature, pulse), and the following areas/symptoms: skin, lymph nodes, head, eyes, ears, nose, throat, respiratory, cardiovascular, abdomen, extremities, musculoskeletal, and neurological.

Vital Signs and Targeted Physical Examination: Vital signs will be collected at each study visit. A targeted physical examination may be conducted at any study visit based on interim medical history.

Adverse Events Assessments: Subjects will be asked if they have any new symptoms since the prior visit.

7.2 Laboratory Evaluations

7.2.1 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed by the University of Iowa Clinical Pathology Laboratory.

Specific tests to be performed are described below:

Hematology includes: hemoglobin, WBC count with differential (eosinophils, neutrophils), platelets, prothrombin time and partial thromboplastin time

Clinical chemistry includes: Na, K, Cl, CO2, urea nitrogen, creatinine, ALT, AST, total bilirubin

Urinalysis will be performed by dipstick testing for proteinuria and glucose in the research clinic. Confirmatory testing may be sent to the University of Iowa Clinical Pathology Laboratory for reflectance spectrophotometry analysis. Note: Urinalysis should be deferred if a participant is menstruating, but should be performed as soon as possible.

One or more of the laboratory parameters may be repeated at any time during the study as determined by the PI, if indicated by an AE. A clinically significant abnormal value should be repeated within 10 days if possible and followed up as clinically relevant.

7.2.2 Special Assays or Procedures

The following PK parameters will be analyzed at Dr. Daryl Murry's lab at the University of Iowa.

- Maximum plasma concentration (C_{max})
- Time to C_{max} (T_{max})
- Elimination rate constant (λ_z)
- Elimination half-life ($t_{½}$)
- Area under the curve to the final sample (AUC_{0-t})
- Area under the curve to infinity (AUC_{∞})
- Oral clearance (CL/F)
- Oral volume of distribution (Vz/F)

Blood samples for PK analysis will be collected in tubes containing sodium heparin as the anticoagulant at baseline (prior to product administration), at 1, 2, 4, 6, 8, 10, 12, 24 hrs, and Days 2, 3, 4, 6, 8 and 15 days after dosing. The blood samples (10 mL) will be placed on ice after draw, and centrifuged within 1 hour at 4-8°C at approximately 3000 rpm for 15 min. The plasma will then be collected and stored frozen at –80°C until analyzed. Urine for oxfendazole, metabolites, and creatinine will be collected. Urine for PK analysis will be collected at baseline (prior to product administration) and for the first 24 hours after product administration with specific collections times of urine for oxfendazole, 0-4, 4-8, 8-12, 12-24. A urine creatinine value will be tested on the 12-24 hours sample and used to calculate creatinine clearance. Spot urine samples will be collected at 24 (+ 8 hrs) and on Day 3 after dosing; 10 mL will be saved, aliquoted and stored at -80°C until analyzed. After the study of each cohort is completed, the collected plasma and urine samples will be shipped to the analytical lab. Validated methods will be used to assay the oxfendazole concentration in each sample.

7.2.3 Specimen Preparation, Handling, and Shipping

Instructions for specimen preparation, handling, storage, and shipping are included in the MOP.

8 ASSESSMENT OF SAFETY

8.1 Specification of Safety Parameters

Safety outcome measures are defined in Section 3.2 and include the rate of SAEs and non-serious severe AEs.

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

8.2.1 Adverse Events

Adverse Event (AE): International Conference on Harmonisation (ICH) E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

All AEs, including solicited systemic (subjective and quantitative) reactions, not meeting the protocol-defined criteria for SAEs will be captured on the appropriate data collection form and electronic case report form (eCRF). Information to be collected for unsolicited AEs includes event description, date of onset, licensed study physician's assessment of severity and relationship to study product and alternate etiology (if not related to study product) (assessed only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator), date of resolution of the event, seriousness and outcome. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to resolution.

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

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

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

Severity of Event: All AEs will be assessed by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or appropriate sub-investigator using a protocol-defined grading system (see Section 9.2.2). For events not included in the protocol-defined grading system, the following guidelines will be used to quantify severity:

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

The severity of systemic and clinical laboratory adverse events will be assessed according to toxicity grading scales taken directly or adapted from the DMID Guidance for Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers. ECG abnormalities will be assessed as per Appendix C.

Relationship to Study Product: The study clinician's assessment of an AE's relationship to study product is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. The relationship to study product must be assessed for all AEs using the terms: related or not related. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used:

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

8.2.2 Adverse Events

Subjects will be queried at each visit as to whether they have experienced any new symptoms or adverse events. Common events that may be encountered are listed below. Vital signs including temperature, pulse and blood pressure will be recorded at each visit. Please refer to the toxicity table in Appendix B for grading of adverse events.

8.2.3 Serious Adverse Events

Serious Adverse Event (SAE):

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

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

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

All SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE form and eCRF.
- Followed through resolution or stabilization by a study physician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Reviewed and evaluated by an Independent Safety Monitor (ISM), the SMC (periodic review unless related), DMID personnel including the medical monitor, and the IRB.

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

The site principal investigator or appropriate sub-investigator is responsible for reporting all AE/SAEs that are observed or reported during the study, regardless of the relationship to study product. AE/SAEs, abnormal clinical laboratory test values, or abnormal clinical findings will be documented, reported, and followed appropriately.

8.3 Reporting Procedures

Reporting of Adverse Events:

AEs will be documented from the time of receipt of study drug on Day 1 (Visit 02) through approximately 14 days after receipt of study product.

SAEs will be documented from the time of receipt of study drug on Day 1 (Visit 02) through approximately 14 days after receipt of study product.

8.3.1 Serious Adverse Events

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

DMID Pharmacovigilance Group
Clinical Research Operations and Management Support (CROMS)
6500 Rock Spring Dr. Suite 650
Bethesda, MD 20814, USA

SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)
SAE FAX Phone Number: 1-800-275-7619 (US) or 1-301-897-1710 (outside US)
SAE Email Address: PVG@dmidcroms.com

Other supporting documentation of the event may be requested by the DMID Pharmacovigilance Group and should be provided as soon as possible.
The DMID medical monitor and clinical protocol manager will be notified of the SAE by the DMID Pharmacovigilance Group. The DMID medical monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct.

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

8.3.2 Regulatory Reporting for Studies Conducted Under DMID-Sponsored IND

Following notification from the investigator, DMID, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. DMID will report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event. DMID will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that

the information qualifies for reporting as specified in 21 CFR Part 312.32. DMID will also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information. Relevant follow-up information to an IND safety report will be submitted as soon as the information is available. Upon request from FDA, DMID will submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

All serious events designated as "not related" to study product(s), will be reported to the FDA at least annually in a summary format.

8.3.3 Reporting of Pregnancy

Not applicable. Females of childbearing potential are excluded from enrollment in the study.

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

AEs and SAEs will be followed from the time of the first receipt of study drug Day 1 (Visit 02) through the last subject's study visit.

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

If the site principal investigator or appropriate sub-investigator becomes aware of a sign or symptom and the site principal investigator or appropriate sub-investigator decides to bring the subject in for an evaluation to determine etiology, then the site principal investigator or appropriate sub-investigator, at their own discretion, can determine what further testing is appropriate.

Follow-up procedures, evaluations, and outcomes will be recorded on the appropriate data collection form.

8.5 Halting Rules

Two sentinel subjects (1 study drug and 1 placebo) will be dosed and monitored 48 hours for adverse events prior to enrolling the remaining subjects in each cohort. If no drug-related SAE or grade 3 study drug related laboratory AE occurs in the sentinel subjects after 48 hours of observation, the remainder of the cohort may proceed with dosing.

An SRC composed of the Protocol Principal Investigator and Independent Safety Monitor will review blinded safety data for each completed cohort. Each new cohort will be dosed only after the 2-week safety data for the preceding group have been reviewed for the following events:

- The SRC will evaluate the safety data from each dose group and will allow continuation if there are no product related grade 3 AEs or if there are fewer than two product related grade 2 AEs identified.

Enrollment, dosing and study procedures will be halted for SMC review/recommendation if any of the following are reported:

- Any death occurring after administration of study drug through the subject's last study visit that was not the result of trauma or accident, regardless of relatedness to study product.

- Any subject experiences laryngospasm, bronchospasm, or anaphylaxis within 24 hours after administration of study product.

- Any subject experiences a study drug-related Stevens Johnson Syndrome.

- Two or more subjects experience generalized urticaria within 72 hours after administration of study product.

- Any subject experiences a study drug-related SAE from the time of receipt of study drug through the subject's last study visit.

- Any subject develops new EKG changes that are deemed significant by a reviewing cardiologist.

- Any subject develops grade 3 laboratory abnormalities deemed related to the study drug.

- The SRC members are not unanimous in their agreement to proceed to the next dosing group or cannot assess or do not unanimously agree on the relatedness of the adverse event to the study product.

If any of the halting rules are met following any subject receipt of study drug, the study will not continue with the remaining enrollments without a review by and recommendation from the SMC to proceed.

DMID retains the authority to suspend additional enrollment and study interventions/administration of study product during the entire study, as applicable.

8.6 Safety Oversight (ISM, SRC, SMC)

8.6.1 Independent Safety Monitor (ISM)

The ISM is a physician with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. The ISM will review SAEs and other AEs as needed and provide an independent assessment to DMID. The University of Iowa will have an ISM with experience in infectious diseases or internal medicine.

8.6.2 Safety Review Committee (SRC)

An SRC composed of the Protocol Principal Investigator and Independent Safety Monitor will review blinded safety data for each completed cohort. Each new cohort will be dosed only after the 2-week safety data for the preceding group have been analyzed.

8.6.3 Safety Monitoring Committee (SMC)

The SMC is an independent group of experts that advises DMID and the study investigators for many Phase 1 and smaller Phase 2 trials. The primary responsibility of the SMC is to monitor subject safety. The SMC is external to DMID, composed of at least three voting members. The SMC will consist of members with appropriate expertise to contribute to the interpretation of the data from this trial. Its activities will be delineated in an SMC charter that will delineate membership, responsibilities, and the scope and frequency of data reviews.

The SMC will review the safety data at the request of the SRC and if any of the halting rules are met.

The SMC will operate on a conflict-free basis independently of the study team. DMID and the SMC may convene ad hoc meetings of the SMC according to protocol criteria or if there are concerns that arise during the study. The ISM or principal investigator may request DMID to convene an ad hoc SMC meeting if a safety concern is identified. The SMC will have access to unblinded data during its closed session, if applicable.

A computerized system will be used to acquire any data regarding halting criteria throughout the study. If any of the halting rules are met, the study will not proceed with the remaining enrollments without a review by the SMC. After its assessment, the SMC will recommend continuation, modification, or termination of the clinical trial.

9 CLINICAL MONITORING

9.1 Site Monitoring Plan

Site monitoring will be conducted to ensure that human subject protection, study procedures, laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, ICH/GCP guidelines and applicable regulatory requirements, and that the study is conducted in accordance with the protocol and sponsor's standard operating procedures. The DMID or its designee will conduct site-monitoring visits as specified in the monitoring plan.

Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, CRFs, informed consent forms, medical and laboratory reports, and protocol compliance. Study monitors will meet with investigators to discuss any problems and actions to be taken and document visit findings and discussions.

10 STATISTICAL CONSIDERATIONS

10.1 Study Hypotheses

The primary objective of the study is to assess the safety and tolerability of oxfendazole in healthy males and non-childbearing females adults aged 18-45 years. The secondary objectives of the study are to assess the pharmacokinetic profile of oxfendazole and to assess the metabolism of oxfendazole.

Primary outcome measures include:

- The rate of serious adverse events (SAEs) related to oxfendazole.
- The rate of severe (Grade 3) adverse events within 7 days following study drug administration in each dosage group.
- The rate of severe (Grade 3) adverse events within 14 days following study drug administration in each dosage group considered related to oxfendazole.

Secondary outcome measures include:

- Plasma Cmax, Tmax, AUC , t1/2 of oxfendazole for each dosage group.
- Plasma and urine concentrations of oxfendazole fenbendazole and oxfendazole sulfone at time points specified in Appendix A Schedule of Events and described in Section 4 Study Design relative to oral dosing.

10.2 Sample Size Considerations

Sample Size Calculations for Safety: The goal of the safety evaluation for this dose-escalation trial is to identify safety concerns associated with oxfendazole. The probability of detecting at least one event for a number of true underlying event rates for 3 potential sample sizes is listed in Table 4. A sample size of 8 will give at least an 80% probability of observing at least 1 event if the true underlying event rate is at least 18%. Sample sizes below 8 will have less than 80% probability of observing such events while a sample size of 10 can detect events with a true rate of 15% with the same probability. Additionally, a sample size of 8 subjects per trial will exclude events occurring in approximately more than 31% of subjects (i.e. the upper bound of an exact one-sided 95% confidence interval is 0.31). The sample of size 8 is consistent for the goals of this study, will provide an adequate basis for safety estimates of each dose and will allow only preliminary safety information relevant to progression to larger trials.

Table 4: Probability of observing at least one event for several true event rates and the event rates which cannot be ruled out if no events are observed.

True Event Rate	Probability of Observing 1 or more events		
	N = 5	**N = 8**	**N = 10**
0.05	23%	34%	40%
0.10	41%	57%	65%
0.18	63%	80%	86%
0.25	76%	90%	94%
	Upper Bound for 95% CI if no event observed		
	N = 5	N = 8	N = 10
	45%	31%	26%

10.3 Planned Interim Data Review

10.3.1 Safety Review

Safety data will be reviewed by the SRC and SMC as outlined in Section 8.

10.3.2 Pharmacokinetic Data Review

The study is a rising dose safety/tolerance study in which plasma is collected for analysis of oxfendazole, fenbendazole and oxfendazole sulfone levels. The primary aim is to determine to what level single doses can be increased without causing limiting toxicity in normal volunteers. In order to facilitate planning for future product development activities without jeopardizing data integrity for this trial, pharmacokinetic data will be entered into the trial database as they become available. After PK data for a cohort is complete, locked and finalized, these group-level (mean and standard deviations) results can be distributed to the study team. These data may be distributed in limited fashion such as grant applications.

10.4 Final Analysis Plan

The primary analysis will be conducted on data and samples collected through study Day 15 of the last dosage cohort. This study, like other Phase I studies, is exploratory rather than confirmatory; its purpose is to estimate event rates and patterns of pharmacokinetic profiling and the metabolism of oxfendazole rather than to test formal statistical hypotheses. Estimates will be presented with their 95% confidence intervals for safety endpoints. Descriptive approaches will be used to meet the protocol objectives as stated in this protocol. Results will be presented in tabular format, as well as graphically when appropriate. Formal comparisons between dose groups will not be made.

Statistical Analysis of PK

PK parameters for oxfendazole will be calculated using non-compartmental analysis. Only plasma concentrations greater than the respective lower limits of quantitation (LOQ) for the assay will be used in the PK analysis.

The maximum plasma concentration (C_{max}) and time to C_{max} (T_{max}) will be taken from the data description. The elimination rate constant, λ_z, will be calculated as the negative of the slope of the terminal log-linear segment of the plasma concentration-time curve. The range of data to be used for each subject and treatment will be determined by visual inspection of a semi-logarithmic plot of concentration vs. time, but will include at least three plasma concentration-time points. Elimination half-life ($t_{½}$) will be calculated according to the following equation:

$$t½ = \frac{0.693}{\lambda z}$$

Area under the curve to the final sample with a concentration ≥ LOQ (AUC_{0-t}) will be calculated using the linear trapezoidal method and extrapolated to infinity using

$$AUC_{\infty} = AUC_{0-t} + \frac{C_{tf}}{\lambda z}$$

where C_{tf} is the final concentration ≥ LOQ.

Oral clearance (CL/F) and volume of distribution (Vz/F) will be calculated according to

$$CL/F = \frac{Dose}{AUC_{(0-\inf)}} \text{ and } Vz/F = \frac{Dose}{\lambda z \times AUC_{(0-\inf)}}.$$

All PK calculations and graphs of individual subject data will be done using appropriate computer software, as determined by the sponsor.

Listing of individual subject plasma concentrations, actual blood sampling times, PK parameters, and graphs of concentration vs. time will be prepared by dosing cohort. Plasma concentrations and PK parameters will be summarized by and compared among dosing cohorts using descriptive statistics. The relationship between C_{max} and AUC_{∞} and dose, i.e., dose proportionality, will be examined using the power model, i.e.,

$$P = a \times Dose^{b}$$

where P represents the parameter and a and b are constants. A value of b of approximately 1 indicates linear PK.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

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

Data collection forms, most of which serve as source documents for this study, will be derived from the electronic CRF and provided by the Statistical and Data Coordinating Center (SDCC) to record and maintain data for each subject enrolled in the study. All data collection forms should be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue ink is required to ensure clarity of reproduced copies. When making a change or correction, cross out the original entry with a single line and initial and date the change. Do not erase, overwrite, or use correction fluid or tape on the original.

Data reported in the eCRF derived from the data collection forms should be consistent with the source documents or the discrepancies should be explained.

The sponsor will provide guidance to investigators on making corrections to the data collection forms and eCRFs.

12 QUALITY CONTROL AND QUALITY ASSURANCE

Following a written DMID-accepted site quality management plan, the investigational site is responsible for conducting routine quality assurance and quality control activities to internally monitor study progress and protocol compliance. The PI will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. The PI will ensure all study personnel are appropriately trained and applicable documentation is maintained on site. DMID-designated clinical monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, ICH/GCP guidelines, and the applicable regulatory requirements. Clinical monitoring reports will be submitted to DMID.

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

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 Ethical Standard

The study will be conducted according to ICH GCP, the Declaration of Helsinki and US 21 CFR Part 50 - Protection of Human Subjects, and Part 56 - Institutional Review Boards. An Independent Safety Monitoring Committee will be established prior to commencing the program. The principles of informed consent in the current edition of the Declaration of Helsinki and other related documents will be implemented before any protocol-specified procedure is carried out. Information will be provided to subjects in both oral and written form. Subjects will be given ample opportunity to inquire about details of the study and have all of their questions answered. The PI and the Co-Investigators have no financial interest in the drugs used in this study.

Monitors under contract to the funding agency will visit the clinical research site to monitor all aspects of the study in accordance with the appropriate regulations. The objectives of a monitoring visit will be: to verify the prompt reporting of all data points, including reporting SAEs; to check availability of signed informed consent; to compare individual subject's records to the source documents (supporting data, laboratory specimen records, and medical records, to include physician progress notes, nurse notes, subject's hospital charts); to ensure protection of study subjects, compliance with the protocol, and to ensure accuracy and completeness of records. The monitors also will inspect the clinical site regulatory files to ensure that regulatory requirements are being followed. During the monitoring visits, the investigator (and/or designee) and other study personnel will be available to discuss the study progress and monitoring visit findings.

The investigator (and/or designee) will make study documents (e.g., consent forms, clinical research forms) and pertinent hospital or clinical records readily available for inspection by the local IRB, the FDA, the site monitors, and the funding agency staff for verification of the study data.

Any changes or additions to the protocol will be submitted to the local and funding agency IRBs for review. A copy of the written approval of the IRBs will be given to the monitor. These requirements for approval will not interfere with immediate action being taken, if needed, to preserve the safety of all subjects included in the study.

Subject consent will be obtained by the study director or his designee.

13.2 Institutional Review Board

Prior to enrollment of subjects into this trial, the approved protocol and the informed consent form will be reviewed and approved by the appropriate IRB. The responsible official for the IRB will sign the IRB letter of approval of the protocol prior to the start of this trial and a copy will be provided to DMID. Notification of the IRB's composition, or the IRB's Federal Wide Assurance number, will be provided to DMID. Should amendments to the protocol be required, the amendments will be written by the sponsor and provided to the investigator for submission to the IRB.

13.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Failure to obtain informed consent via a signed consent form from each subject before enrollment is a serious protocol violation. Before a potential subject is given the written consent form, a study nurse or licensed study clinician will discuss in detail with the individual the nature of the study, randomization, blinding, study procedures, the importance of compliance with study procedures, potential risks and benefits of participation, and the duration of the study. The subject will specifically be told of the risks of oxfendazole suggested by preclinical toxicology studies of oxfendazole or by known toxicity of other drugs of this class, which include risk of liver dysfunction, danger to an unborn child if pregnancy occurs, and effects on reproductive capabilities. The potential subject will be explicitly told that he/she is not obligated to participate and that there will be no penalty for declining to participate, and that he/she may withdraw from the study at any time.

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

This study will be inclusive of all healthy adults who meet the inclusion/exclusion criteria, regardless of religion, sex, or ethnic background. Only individuals, who are 18 to 45 years old, inclusive, will be included at this time. Women of childbearing potential and children are excluded for safety reasons. Prisoners are excluded due to the rigorous study schedule that would not be feasible in an incarcerated population. Should the outcome of this study be deemed acceptable, additional trials may be initiated in other populations.

13.5 Subject Confidentiality

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

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

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

The study monitor, the University of Iowa IRB, applicable regulatory authorities, such as the FDA, or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the site principal investigator. This includes, but is not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this trial. The participating VTEU sites will permit access to such records.

13.6 Study Discontinuation

If the study is discontinued, enrolled subjects will continue to be followed for safety assessments.

Subjects will be compensated for their participation in this study. Compensation will be in accordance with the local IRB's policies and procedures and subject to IRB approval.

13.7 Future Use of Stored Specimens

No future uses of specimens collected during this study are planned. Residual samples from safety laboratory evaluations and assays for PK analysis will be stored at the University of Iowa until all testing has been completed. Each sample will be encoded (labeled) *only* with a barcode and a unique tracking number to protect subject's confidentiality. Samples will be destroyed after all study assays have been completed.

13.8 Data Management Responsibilities

All source documents and laboratory reports must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. Adverse events must be graded, assessed for severity and causality, and reviewed by the site PI or designee.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. During the study, the investigator must maintain complete and accurate documentation for the study.

The EMMES Corporation will serve as the Statistical and Data Coordinating Center for this study and will be responsible for data management, quality review, analysis, and reporting of the study data.

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

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each subject enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained

DMID and/or it designee will provide guidance to investigators on making corrections to the source documents and eCRF.

13.9 Data Capture Methods

Clinical data (including AEs, concomitant medications, and reactogenicity data) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant Internet Data Entry System (IDES) provided by The EMMES Corporation. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

13.10 Types of Data

Data for this study will include clinical, safety, and outcome measures (e.g., clinical laboratory values, adverse events, and pharmacokinetic and metabolic data).

13.11 Timing/Reports

A final report will be prepared following the availability of all the safety, adverse events, and pharmacokinetic data. Interim statistical reports may be generated as deemed necessary and appropriate by DMID. Safety and pharmacological summary reports may be generated for the SMC.

13.12 Study Records Retention

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

13.13 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practice (GCP), or Manual of Procedures requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
5.1 Quality Assurance and Quality Control, section 5.1.1
5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported to DMID, via The EMMES Corporation's IDES or via the TRI/ICON DMID-Clinical Research Operations and Management Support (CROMS) email (protocoldeviations@dmidcroms.com), web-(www.dmidctm.com) or fax-based system (1-215-699-6288).

Note: Those sites participating in trials with a designated 'central unit' will follow the reporting requirements specified in their protocols and MOPs. The 'central unit' will be responsible for submission of the protocol deviation information to TRI/ICON DMID-CROMS.

All deviations from the protocol must be addressed in study subject source documents. A completed copy of the DMID Protocol Deviation Form (TRI/ICON DMID-CROMS or IDES form) must be maintained in the regulatory file, as well as in the subject's source document. Protocol deviations must be sent to the local IRB/IEC per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB/IEC requirements.

Publication Policy

Following completion of the study, the investigator is expected to publish the results of this research in a scientific journal. The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov[55], which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. It is the responsibility of DMID to register this trial in an acceptable registry. Any clinical trial starting enrollment after 01 July 2005 must be registered on or before subject enrollment. For trials that began enrollment prior to this date, the ICMJE member journals will require registration by 13 September 2005, before considering the results of the trial for publication.

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

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SUPPLEMENTS/APPENDICES

APPENDIX A: SCHEDULE OF EVENTS

Study Visit Number	1	2	3	4	5	6	7	8
Study Day (post administration)	D-28 to -1	D1	D2	D3	D4	D6	D8	D15
Visit/Contact Window (Days)	NA	NA	NA	NA	NA	**+/- 1**	**+/- 1**	**+/- 2**
Informed Consent	x							
Inclusion/Exclusion	x	x						
Medical History	x							
Interim Medical History		x						
Concomitant Medications	x	x	x	x	x	x	x	x
Vital signs[1]	x	x	x	x	x	x	x	x
Physical Examination	x	x						
HIV, HBC, HCV Testing	x							
Administration of oxfendazole/placebo[2]		x						
Counseling on avoidance of medications, recreational drugs and alcohol intake	x	x	x	x	x	x	x	

Study Visit Number	1	2	3	4	5	6	7	8
Study Day (post administration)	D-28 to -1	D1	D2	D3	D4	D6	D8	D15
Visit/Contact Window (Days)	NA	NA	NA	NA	NA	**+/- 1**	**+/- 1**	**+/- 2**
Targeted physical exam			x	x	x	x	x	x
Screening and Safety Labs (CBC, Blood Chemistry, Urinalysis)[1,3,4,7]	x[7]	x[4]		X[8]	x[4]		x[4]	x[4]
EKG	x				x		x	x
Blood draw for oxfendazole and metabolites[5]		x	x	x	x	x	x	x
Urine collection for oxfendazole, metabolites and creatinine[6]		x	x	x				
Assess/review for AEs and SAEs		x	x	x	x	x	x	x
Blood Volume for Day (Total Blood Volume for Study)	15 mL (15mL)	105 mL (120mL)	10 mL (130 mL)	10 mL (140 mL)	25 mL (165 mL)	10 mL (175 mL)	25 mL (200 mL)	25 mL (225 mL)

[1] Vital signs and laboratory values will be evaluated using the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials," September 2007.

[2] Volunteers will remain fasting for 2 hours after administration of drug/placebo.

[3] Any abnormal laboratory result arising after administration of oxfendazole, and of moderate or greater severity, will be followed until results return to baseline value or for the duration of safety follow-up.

[4] Safety laboratories include: WBC, absolute neutrophil count, eosinophil count, total platelet count, hemoglobin, sodium, potassium, chloride, bicarbonate, urea nitrogen, creatinine, prothrombin time, partial thromboplastin time, ALT, AST, total bilirubin, urine dipstick for protein and glucose

[5] Blood will be drawn prior to dosing for baseline PK data, and then at, 1, 2, 4, 6, 8, 10, 12, 24 (+ 8 hours), and on Day 3, followed by the indicated visit days. Blood will also be drawn at the final study visit (Day 15).

[6] Urine will be obtained on admission for baseline PK data, and all urine will be collected for the first 24 hours following the schedule of urine collections at 0-4, 4-8, 8-12, 12-24 hours. Spot urine samples will be collected on Days 2 and 3 following drug administration. A urine creatinine value will be tested on the 12-24 hours sample only.

[7] Screening labs include WBC, absolute neutrophil count, eosinophil count, total platelet count, hemoglobin, creatinine, ALT, AST, total bilirubin, random glucose, urine dipstick for protein and glucose

[8] Blood for safety laboratory analysis will be obtained for the two sentinel subjects in each dose group. (WBC, absolute neutrophil count, eosinophil count, total platelet count, hemoglobin, sodium, potassium, chloride, bicarbonate, urea nitrogen, creatinine, prothrombin time, partial thromboplastin time, ALT, AST, total bilirubin)

APPENDIX B: DMID ADULT TOXICITY TABLES
NON-SERIOUS ADVERSE EVENTS

ABBREVIATIONS: Abbreviations utilized in the Tables:
ULN = Upper Limit of Normal IV = Intravenous
LLN = Lower Limit of Normal

Clinical Adverse Events			
VITAL SIGNS	**Grade 1**	**Grade 2**	**Grade 3**
Fever (°C) **	38.0 – 38.4	38.5 – 38.9	>39.0
Fever (°F) **	100.4 – 101.1	101.2 – 102.0	>102.1
** Oral temperature; no recent hot or cold beverages or smoking. A protocol should select either °C or °F for inclusion.			
Tachycardia - beats per minute	101 – 115	116 – 130	> 130 or ventricular dysrhythmias
Bradycardia - beats per minute	50 – 54 or 45-50 bpm if baseline 5-60 bpm. For athletically trained individuals with a pulse 45-49, grade 1 abnormality = pulse 40-44	45 – 49 or 40-44 bpm if baseline 50-60 bpm. For athletically trained individuals with a pulse 45-49, grade 2 abnormality = pulse 35-39	< 45 or <40 bpm if baseline 50-60 bpm. For athletically trained individuals with a pulse 45-49, grade 2 abnormality = pulse less than 35 or pulse 35-45 with symptoms of lightheadedness, exercise intolerance, syncope
Hypertension (systolic)- mm Hg**	141-150	151-160	> 160
Assuming supine position, 10 min at rest conditions, not sleeping subjects, measurements on the same arm and several concordant results.			
Hypertension (diastolic) - mm Hg**	91-95	96-100	> 100
Hypotension (systolic) - mm Hg**	85-89	80-84	< 80
Tachypnea – breaths per minute	23-25	26-30	>30
CARDIOVASCULAR	**Grade 1**	**Grade 2**	**Grade 3**

Arrythmia		Asymptomatic, transient signs, no Rx required	Recurrent/persistent; symptomatic Rx required
Hemorrhage, Blood Loss	Estimated blood loss ≤ 100 mL	Estimated blood loss > 100 mL, no transfusion required	Transfusion required
RESPIRATORY	**Grade 1**	**Grade 2**	**Grade 3**
Cough	Transient- no treatment	Persistent cough;	Interferes with daily activities
Bronchospasm, Acute	Transient; no treatment; 71% - 80% FEV1 of peak flow	Requires treatment; normalizes with bronchodilator; FEV1 60% - 70% (of peak flow)	No normalization with bronchodilator; FEV1 <60% of peak flow
Dyspnea	Does not interfere with usual and social activities	Interferes with usual and social activities, no treatment	Prevents daily and usual social activity or requires treatment
GASTROINTESTINAL	**Grade 1**	**Grade 2**	**Grade 3**
Nausea	No interference with activity	Some interference with activity	Prevents daily activities
Vomiting	No interference with activity or 1 - 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity or requires IV hydration
Diarrhea	2 - 3 loose or watery stools	4 - 5 loose or watery stools	6 or more loose or watery stools or requires IV hydration
Reactogenicity			
SYSTEMIC	**Grade 1**	**Grade 2**	**Grade 3**
Allergic Reaction	Pruritus without rash	Localized urticaria	Generalized urticaria; angioedema or anaphylaxis

Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity
All Other Conditions	**Grade 1**	**Grade 2**	**Grade 3**
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention

Laboratory Adverse Events			
Blood, Serum, or Plasma *	**Grade 1**	**Grade 2**	**Grade 3**
Sodium – Hyponatremia mEq/L	132 – <LLN	130 – 131	<130
Sodium – Hypernatremia mEq/L	>ULN – 148	149 – 150	>150
Potassium – Hyperkalemia mEq/L	>ULN – 5.2	5.3 – 5.4	>5.4
Potassium – Hypokalemia mEq/L	<LLN-3.1	<3.1 – 3.0	<3.0
CO_2	1-2 mEq/L above or below normal	3-4 mEq/L above or below normal	5 or more mEq/L above or below normal
Chloride	1-3 mEq/L above or below normal	4-5 mEq/L above or below normal	6 or greater above or below normal
Glucose – Hypoglycemia mg/dL	65 – 67	55 – 64	<55
Glucose – Hyperglycemia Fasting – mg/dL	>ULN - 120	121 – 130	>130
Glucose – Hyperglycemia Random – mg/dL	140 – 159	160 – 200	>200
Blood Urea Nitrogen mg/dL	23-26	27 – 31	> 31
Creatinine – mg/dL	>ULN – 1.7	1.8 – 2.0	>2.0
Calcium – hypocalcemia mg/dL	8.0 – <LLN	7.5 – 7.9	<7.5
Calcium – hypercalcemia mg/dL	>ULN – 11.0	11.1 – 11.5	>11.5
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	<1.1

Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	<2.0
CPK – mg/dL	400-1000	1001-1500	>1500
Albumin – Hypoalbuminemia g/dL	2.8 – 3.0	2.5 – 2.7	< 2.5
Total Protein – Hypoproteinemia g/dL	5.2 – <LLN	5.0 – 5.4	< 5.0
Alkaline phosphate – U/L	132-240	241– 360	>360
AST U/L	44 – 105	106-175	>175
ALT U/L	44 – 105	106-175	>175
Bilirubin (serum total) mg/dL	1.3 - 2.0	2.1 - 2.5	> 2.5
Bilirubin – when ALT ≥105 (Hy's law)	1.3 -1.5	1.6 – 2.0	> 2.0
Amylase- U/L	200-270	271-360	>360
Lipase- U/L	176-270	271-360	>360
Hemoglobin (Female) - g/dL	11.0 – 11.5	9.5 – 10.9	< 9.5
Hemoglobin (Male) - g/dL	12.0 – 12.5	10.0 – 11.9	<10.0
WBC Increase - cell/mm3	11,001 – 15,000	15,001 – 20,000	> 20,000
WBC Decrease - cell/mm3	2,500 – 3,500	1,500 – 2,499	< 1500
Lymphocytes Decrease - cell/mm3	750 – 1,000	500 – 749	< 500
Neutrophils Decrease - cell/mm3	1,500 – 2,000	1,000 – 1,499	< 1000
Eosinophils - cell/mm3	500-750	751-1500	> 1500
Platelets Decreased - cell/mm3	120,000 – 130,000	100,000 – 119,999	<100,000
PT – seconds (prothrombin time)	> ULN-14.4	14.5 – 15.7	> 15.7
PTT – seconds (partial thromboplastin time)	>ULN-42.1	42.2– 50.0	> 50.0
Fibrinogen increase - mg/dL	>ULN – 500	501 – 600	> 600
Fibrinogen decrease - mg/dL	<LLN – 140	125 – 139	<125
Urine *	**Grade 1**	**Grade 2**	**Grade 3**
Protein	1+	2+	>2+
Glucose	1+	2+	>2+
Blood (microscopic) - red blood cells per high power field (rbc/hpf)	5-10	11-50	> 50 and/or gross blood

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters.
* Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

APPENDIX C: GRADE THRESHOLDS FOR EKG

		Grades		
Parameter	**Origin**	**1**	**2**	**3**
PR interval increase (ms)*	CPI	220 to 250 and increase exceeding 20 ms	>250	Mobitz 2 or syncope [21]
QT_c interval increase (young male) using the most accurate QT_c formula (ms)*		ULNR to 475 ms and increase exceeding 40 ms	476 to 499	>500 ms, or QTC over 460 and increase exceeding 60 ms
QT_c interval increase (women)*		Same as male plus 20 ms		

*Assuming supine position, 10 min at rest conditions, not sleeping subjects and several concordant results. ULNR, Upper limit of normal range; LLNR, Lower limit of normal range; CPI, Club phase I task force.

APPENDIX D: UNIVERSITY OF IOWA NORMAL LABORATORY VALUES

	Male	Female
Complete Blood Count		
WBC	3.7-10.5 k/mm³	3.7-10.5 k/mm³
RBC	4.5-6.2 millions/mm³	4.0-5.2 millions/mm³
Hemoglobin	13.2-17.7 g/dl	11.9-15.5 g/dl
Platelets	150-400 k/mm³	150-400 k/mm³
Hemogram plus Automated Differential		
Neutrophils	2188-7800/mm³	Same
Eosinophils	40-390/mm³	Same
BUN	10-20 mg/dl	Same
Creatinine	0.6-1.2 mg/dl	0.5-1.0 mg/dl
Alanine Aminotransferase (ALT)	0-41 u/l	0-33 u/l
Aspartate Aminotransaminase (AST)	0-40 u/l	0-32 u/l
Chloride	95-107	Same
CO_2	22-29 mEq/L	Same
Potassium	3.5-5.0	Same
Sodium	135-145	Same
Total Bilirubin	<=1.2 mg/dL	Same
Prothrombin Time	9-12 seconds	Same
Partial Thromboplastin Time	22-31 seconds	Same
Glucose (fasting)	65-99	Same
Urinalysis, Routine Screen (using Reflectance Spectrophotometry)	Specific gravity: 1.000-1.029; pH: 5.0-9.0, Dipstick negative for protein, hemoglobin, bilirubin, urobilinogen, ketones, glucose, leukocyte esterase and nitrite	Same
Urine Microscopy	0-5 WBC, 0-2 RBC	Same
Pregnancy Test		Positive = pregnant; Negative = not pregnant
Hepatitis B Surface Antigen	Negative	Same
HIV Types 1&2 Antibody	Non-Reactive	Same
Hepatitis C Virus Antibody, Version 2.0	Negative	Same