A Phase 1 Open Label, Multiple Ascending Dose Study of Oxfendazole in Healthy Adult Volunteers

DMID Protocol Number: 16-0005

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Version Number: 4.0

24 July 2017

STATEMENT OF COMPLIANCE

This trial will be conducted in compliance with the protocol, International Conference on Harmonisation guideline E6: Good Clinical Practice: Consolidated Guideline, the applicable regulatory requirements from US Code of Federal Regulations (CFR) (Title 45 CFR Part 46 and Title 21 CFR including Parts 50 and 56) concerning informed consent and Institutional Review Board regulations, and the NIAID 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 subinvestigators 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 Investigator: Patricia Winokur, MD

Signed: _____ Date: _____

Name
Title

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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
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
eCRF	Electronic Case Report Form
EKG	Electrocardiogram
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability and Accounting Act
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
OCRA	Office of Clinical Research Affairs, NIH, DHHS
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
WHO	World Health Organization

PROTOCOL SUMMARY

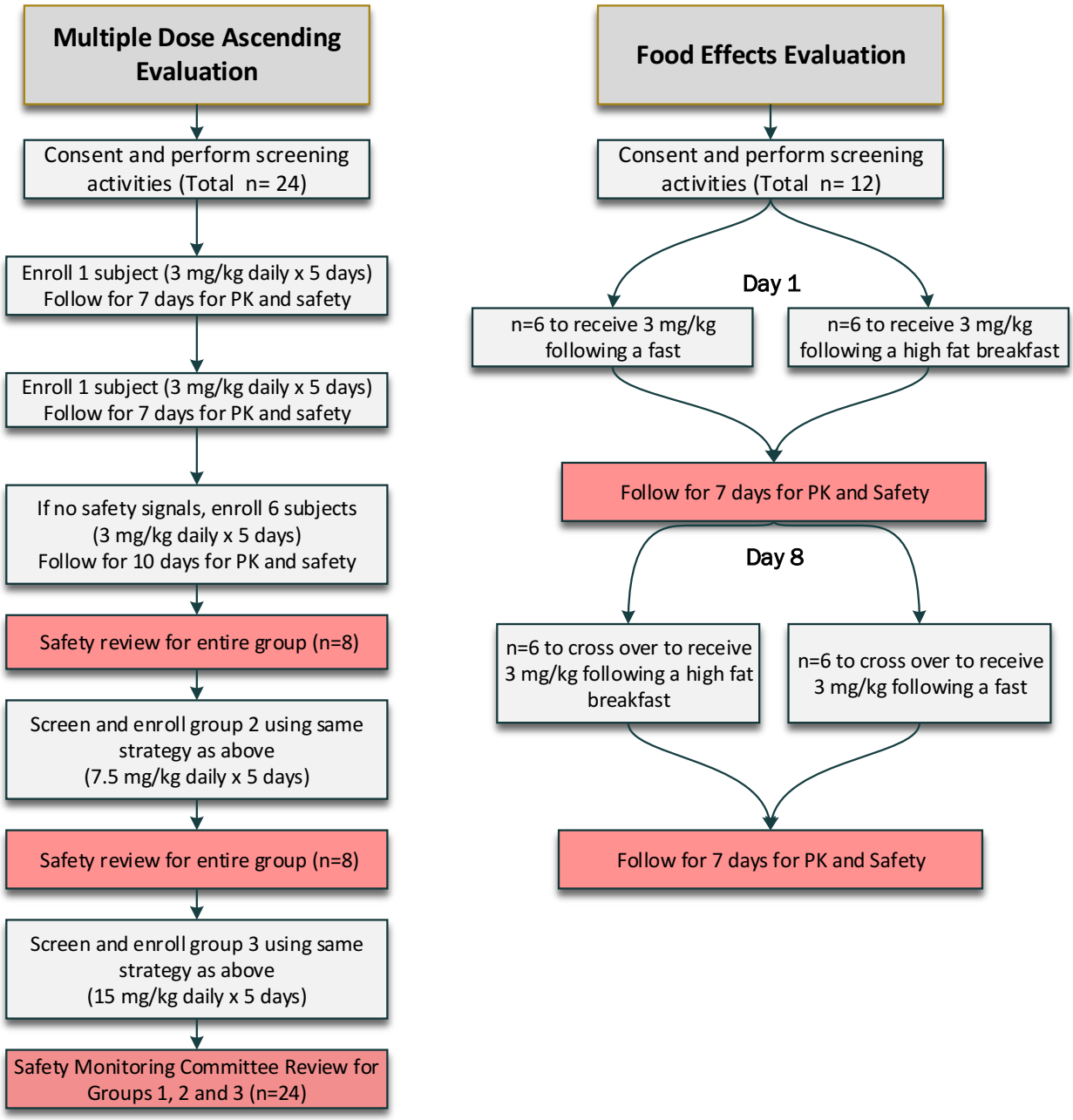
Title:	A Phase 1, Open-Label, Multiple Ascending Dose Study of Oxfendazole in Healthy Adult Volunteers
Phase:	I
Population:	Up to 36 healthy males and nonpregnant females, ages 18-45, recruited from around Iowa City, IA
Number of Sites:	One site, the University of Iowa
Study Duration:	Approximately 12 months
Subject Participation Duration:	Approximately 6 weeks
Description of Agent or Intervention:	Two to five oral doses of an aqueous suspension of oxfendazole, a benzimidazole carbamate antiparasitic drug
Objectives:	Primary: • To assess the safety of oxfendazole administered daily for five days • To assess the safety of oxfendazole administered as a single dose with or without food Secondary: • To define the multi-dose kinetics of oxfendazole • To determine the effect of food on the kinetics of oxfendazole
Description of Study Design:	This Phase I study is an open label evaluation of the safety and pharmacokinetics of escalating oral doses of oxfendazole (3 mg/kg, 7.5 mg/kg or 15 mg/kg) given daily for five days in healthy volunteers. Up to eight volunteers will be enrolled and receive one oral dose of 3 mg/kg given daily for 5 days. To enhance safety, one sentinel subject will be enrolled and followed for 7 days for defined safety events. A second sentinel subject will then be enrolled and followed for 7 days. If no

predefined safety events are identified, the remaining six subjects in this group will be enrolled. All volunteers will be followed for 10 days and pharmacokinetic, safety laboratory and EKG studies will be performed as outlined in the study visit table in Appendix A. A safety review of the electronic data will be completed and the DMID Medical Monitor will receive a dose escalation report from the Statistical and Data Coordinating Center (SDCC) including whether dose escalation halt criteria were or were not met. If no predefined safety events occur after all eight subjects have completed the day 10 visit, the DMID Medical Monitor will issue approval to proceed with enrollment of the second group of eight subjects will be enrolled to receive five days of 7.5 mg/kg of oxfendazole using the same enrollment plan as outlined above. If no predefined safety events are encountered, the third group of eight subjects will be enrolled to receive five days of 15 mg/kg using the same enrollment plan. A fourth group of 12 subjects will participate in a single dose cross over evaluation of the effects of food on the pharmacokinetics of oxfendazole. Half of these subjects will fast for 8 hours and then will receive a single dose of 3 mg/kg of oxfendazole on day 1. The other half will receive a single dose of 3 mg/kg of oxfendazole following a high fat breakfast. All 12 subjects will be followed for seven days and on day 8 each subject will cross over to receive drug following a high fat breakfast or following an 8 hour fast and will be followed for another seven days. Pharmacokinetic studies will be performed for 24 hours following each dose of oxfendazole.

Group	N	Study Dose	Timing of Study Dosing
1	8	3 mg/kg	Days 1-5
2	8	7.5 mg/kg	Days 1-5
3	8	15 mg/kg	Days 1-5
4	12	3 mg/kg	Days 1 and 8 Dose received following a fast (n=6) or high fat meal (n=6) on Day 1 and crossed over to opposite arm to receive drug following high fat meal or fast on Day 8

Estimated Time to Complete Enrollment: 12 months

***Schematic of Study Design**:



1 KEY ROLES

Refer to ICH E6, Section 6.1
(http://www.fda.gov/downloads/Drugs/Guidance/ucm073122.pdf)

For questions regarding this protocol, contact <<*insert name of appropriate DMID staff*>> at <<*NIAID/DMID (insert contact information)*>>.

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2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

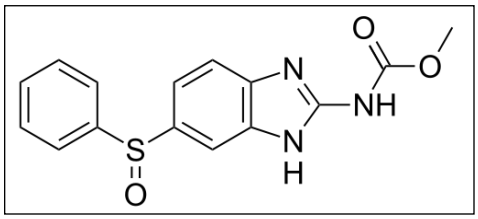
The three major soil transmitted helminthes, *Ascaris lumbricoides* (roundworm), *Necator americanus/Ancylostoma duodenale* (hookworms) and *Trichuris trichiura* (whipworm) are among the most prevalent parasites worldwide. They are highly prevalent in developing countries that suffer from poverty and poor sanitation. It is estimated that these three helminths have an overall prevalence of one billion cases worldwide. Nearly half of these cases result in significant morbidity especially affecting young children (1). Current control measures require the periodic administration of one of the four antihelminthics: mebendazole, albendazole, levamisole or pyrantel. Of these drugs, the benzimidazoles (mebendazole and albendazole) are the most frequently used antihelminthics. However, these drugs show varying efficacy against the array of human helminths. Single oral doses of these compounds are highly effective against *Ascaris lumbricoides*, but have significantly less efficacy for hookworms and *Trichuris trichiura* (2).

Oxfendazole (OXF) is a potent, broad-spectrum antihelminthic drug that is approved and marketed for veterinary use. Oxfendazole is currently marketed for use against lungworms and enteric helminths in beef livestock. In humans, current benzimidazoles include albendazole and mebendazole. Though all of the benzimidazoles show chemical similarities, the compound oxfendazole reaches peak blood levels more slowly following absorption from the intestinal tract than many other benzimidazoles, thereby maintaining effective concentrations for a longer time in both the serum and intestinal tract. This prolonged half-life is attractive for pursuing single dose therapy for certain helminths including uncomplicated cysticercosis. However, even with this more prolonged half-life it is likely that extended therapy will likely be required for the soil transmitted helminthes such as *Trichuris trichiura* and hookworm infections. Given the potentially favorable pharmacokinetics, oxfendazole is an attractive compound for transition to human use and animal and human studies outlined below have begun to define the safety and pharmacokinetic parameters of this compound.

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 (3). The structure consists of the benzimidazole carbamate characteristic of this group of drugs, with a phenylsulphinyl substituent in position 5 (4). Oxfendazole (Synanthic®) is formulated as an aqueous suspension of either 9.06% or 22.5%, manufactured by Boehringer Ingelheim Animal Health. At the current time, only the 22.5% formulation is available, though production of the lower concentration may return in the future.

The introduction of thiabendazole as the first benzimidazole anthelminthic in the early 1960s provided a significant advance in veterinary antiparasitic treatment (7). However, thiabendazole has a short biological half-life, due to rapid hydroxylation of the 5 (8) position of the benzimidazole ring and extensive urinary clearance (9). 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 (10). 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 (11). Thiabendazole, mebendazole and albendazole are currently approved and marketed in the US for treatment of helminth infections in humans.

2.1.1.2 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 (11). They also alter the tubulin-microtubule equilibrium, by binding at the colchicine site in the tubulin dimer (12). Inhibition of tubulin polymerization induces disintegration of the microtubular network in parasites (13).

2.1.1.3 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 mg/kg/day
		Syntex study number(21)	mg/kg/day	mg/m^2/day	

Species	Study	No Effect Dose			
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
Dog	Single dose		1600		864

2.1.1.4 Animal Safety

The potential cardiovascular or toxicity effects of oxfendazole (OXF) were investigated after drug administration to beagle dogs (14). 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 (15). There were no changes in feeding, behavior or physiological measurements (15). 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 (16). Similar dog studies showed no toxicity (16). Fetotoxicity was noted in rats and mice (16).

2.1.2 Human Phase I Safety and Pharmacokinetics

A recent dose escalation study has been performed evaluating 70 healthy adult men and women of non-child bearing potential who were age 18-45 (NCT02234570, DMID 12-0053, unpublished). Seven dose groups were studied (0.5, 1, 3, 7.5, 15, 30 and 60 mg/kg) and each dose group was comprised of 10 subjects of whom eight received study drug and two received placebo. All subjects received a single dose of study drug or placebo and were followed for 14 days for safety and the pharmacokinetics of oxfendazole and metabolites including fenbendazole and oxfendazole sulfone were evaluated in blood and urine. There were no study drug associated serious adverse events identified. Sixteen unsolicited adverse events were experienced by 10 subjects. Six were considered related to the study treatment. Five of the events were mild and included one subject with an increased PR interval 14 days following the dose of study drug, and the remaining events were gastrointestinal events (nausea, loose stools, intestinal gas, and diarrhea, all of which occurred in the 30 or 60 mg/kg dose groups. There was one event, a sore throat that was considered moderate in intensity. Mild to moderate laboratory events were seen in hematology and chemistry tests. There were no patterns identified related to timing of the abnormal laboratory studies or dose of oxfendazole and the placebo group had similar rates of abnormal laboratory values.

The median time of maximum concentration (T_{max}) occurred at 2 hours and the geometric mean maximum concentration (C_{max}) ranged from 943.9-6768.4 ng/mL. The exposure was non-linear, plateauing at 15 mg/kg. The half-life ($t_{1/2}$) was consistent between groups and ranged from 8.5-11 hours. The overall fraction of drug excreted in the urine was very low and the geometric mean AUC_{0-t} for the sulfone metabolite was 11.5-15% of oxfendazole AUC_{0-t} while fenbendazole AUC_{0-t} was less than 1% of oxfendazole AUC_{0-t} for each dose group.

2.2 Rationale

The first Phase 1 study outlined above demonstrated the safety of a single dose of oxfendazole and established the pharmacokinetic parameters for the drug. Though single dose therapy for some helminths may be adequate, more resistant soil transmitted species such as *Necatur americanus* and *Trichuris trichiura* and even more complicated neurocysticercosis may require extended therapy. The purpose of this study is to establish the safety and pharmacokinetic activity of multiple doses of oxfendazole. In this study, three dose levels each given daily for five days will be studied in a dose escalation design.

The other important parameter that remains unanswered is the effect of food on the absorption of oxfendazole. Therefore, this study will also include an arm that includes a single dose cross over design in which individuals will receive drug following an 8 hour fast or following a high fat meal.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Oxfendazole has been studied in a single human phase I trial in doses that are similar to those proposed in this study. Seventy healthy adults were evaluated in a dose escalation trial where each individual received a single dose of oxfendazole with dosage levels ranging from 0.5 to 60 mg/kg. The drug was well tolerated though a few subjects experienced mild gastrointestinal symptoms (mild nausea and short duration diarrhea) seen on the day of dosing in the 30 mg/kg and 60 mg/kg dosage levels. One individual had a grade 1 increase in the PR interval seen on EKG 14 days after the study drug had been administered. Fifteen subjects reported 37 abnormal hematology results, 27 were mild, 7 were moderate and 3 were severe. All three severe results were elevated APTT levels experienced by a single subject who had the abnormal PTT prior to receiving study drug. He was evaluated and found to have an acquired factor XI or XII deficiency that was not related to study drug. A total of 64 abnormal biochemistry results were reported by 34 subjects of which 58 were mild and 6 were moderate. There was no association between the timing of study drug the dose of study drug, and the placebo group demonstrated similar rates of abnormal laboratory tests and all abnormalities resolved.

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. Albendazole has also 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 %.

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 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.

Men will be counseled to use condoms and women will be counseled to avoid pregnancy attempts for 4 months following drug administration. It is unknown if Oxfendazole pose any risks to an unborn child.

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 is no known benefit to this study product. However, oxfendazole has antiparasitic activity in animals and may have similar activities in humans. There is the potential that participation in this study could have societal benefits as knowledge about new antiparasitic agents could help in the creation of new drugs for difficult to treat helminthic infections.

3 OBJECTIVES

3.1 Study Objectives

Primary:

- To assess the safety of oxfendazole administered daily for five days
- To assess the safety of oxfendazole administered as a single dose with or without food

Secondary:

- To define the multi-dose kinetics of oxfendazole
- To determine the effect of food on the kinetics of oxfendazole

3.2 Study Outcome Measures

3.2.1 Primary endpoint:

- The rate of adverse events (AEs) related to oxfendazole within 10 days of receipt of oxfendazole given for 5 sequential, daily oral doses of either 3, 7.5 or 15 mg/kg
- The rate of adverse events (AEs) related to oxfendazole within 7 days of receipt of oxfendazole given as a single daily dose of 3 mg/kg on days 1 and 8 either following an 8 hour fast or following a high fat meal.

3.2.2 Secondary endpoints:

- Plasma Cmax, Tmax, AUC, $T_{1/2}$ of oxfendazole at specified time points following each dose of a 5 day daily regimen of either 3, 7.5 or 15 mg/kg
- Plasma Cmax, Tmax, AUC, $T_{1/2}$ of oxfendazole at specified time points following a single dose of oxfendazole of 3 mg/kg on days 1 and 8 administered after an 8 hour fast or after a high fat meal.

4 STUDY DESIGN

This Phase I study is an open label multiple ascending dose evaluation of the safety and PK of oxfendazole (3, 7.5, or 15 mg/kg) in healthy adult men and nonpregnant women aged 18-45 (inclusive) followed by a single dose cross over trial evaluating the safety and pharmacokinetics of a single dose of oxfendazole (3 mg/kg) given following an 8 hour fast or following a high fat meal. In the multiple ascending dose evaluation, each dose group will be comprised of eight volunteers. In the food effects evaluation, evaluating the effects of food on drug absorption, 12 subjects will be enrolled into the single dose cross over group where half of the subjects will initially receive a single dose of 3 mg/kg of oxfendazole following an 8 hour fast and the other half will receive a single dose of 3 mg/kg of oxfendazole following a high fat meal. Subjects will then cross over to receive a single dose following a high fat breakfast or fasting period (water is permitted). All subjects will have received a single dose of oxfendazole (3 mg/kg) following both a fasting period and a meal.

For the multiple ascending dose evaluation, each subject in the first dose group (3 mg/kg) will receive an oral daily dose of oxfendazole for five sequential days and will be monitored for a total of 10 days. Each subject will be followed with blood, urine and EKG studies for safety and will provide plasma samples for oxfendazole PK studies as outlined in the study visit schedule in Appendix A. To enhance safety, one sentinel subject will be dosed for five days and monitored for 7 days from the time of the first dose for predefined adverse events, which will include any drug related SAEs, any study drug-related Grade 3 AEs or laboratory abnormalities or two study drug-related Grade 2 AEs or laboratory abnormalities in the same laboratory parameter. If there are no predefined safety events, a second sentinel subject will be enrolled and followed for a total of 7 days. If there are no predefined safety signals identified for either of these two sentinel subjects, the remaining subjects in the group will be enrolled.

After all eight subjects have completed the 10 day follow up period, an electronic safety review of the electronic data will be performed and the SDCC will issue a report to DMID stating that the predefined halting rules have or have not been met. If none of the predefined safety events (any study drug related SAE, any study drug related Grade 3 AE or laboratory abnormality or two study drug related Grade 2 AEs or laboratory abnormalities in the same laboratory parameter have occurred (one study drug related two sequential subjects (one at a time with 7 days between each subject) DMID will approve enrollment into the second dose group (7.5 mg/kg oxfendazole daily x 5 days) and will be monitored for a total of 7 days each for predefined adverse events prior to enrolling the remaining subjects in the group. After the 10 day follow up period has been completed for group 2, an electronic safety review will be completed and if no predefined events have occurred two sequential subjects (one at a time with 7 days between each subject) will be enrolled into the third dose group (15 mg/kg oxfendazole daily x 5 days) and will be monitored for a total of 7 days each for predefined safety events prior to enrolling the remaining subjects in the group.

For the multiple ascending dose evaluation, between 8 and 24 subjects will be enrolled. This number should be small enough to perform the study safely and efficiently, yet large enough for an estimation of the oxfendazole PK and the identification of any common side effects of oxfendazole following multiple doses.

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, platelet count, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, random glucose, urine dipstick for protein and glucose, INR and partial thromboplastin time (PTT), hepatitis B surface antigen, hepatitis C antibody, and human immunodeficiency virus serology (HIV). 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 and vital signs, including oral temperature, blood pressure and pulse will be obtained. A review of medication history since the screening visit will be obtained and a 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, platelet count, creatinine, Na, K, Cl, CO_2, blood urea nitrogen, alanine aminotransferase (ALT), aspartate aminotransferase (AST), INR and PTT, total bilirubin, and urine dipstick for protein and glucose).

Subjects will be administered oxfendazole by a study nurse or investigator on days 1, 2, 3, 4 and 5. Subjects will be fasting (water is permitted) for eight hours prior to, and for two hours after, the administration of drug. On the 1st and 5th day of drug administration intensive blood sampling will be performed for PK studies (pre-dose and 30 minutes, 1, 2, 3, 4, 6, 9, and 12 hours following the dose). On days 2, 3 and 4, blood sampling for PK studies will be performed prior to each dose and 2 hours after each dose. On day 6, blood sampling for PK studies will be performed approximately 24 hours following the dose on day 5. Monitoring will start immediately after dosing and will continue for 10 days. Safety laboratories will be performed on days 1, 3, 5, 8 and 10. EKG studies will be performed at screening, two hours after doses on days 1, 3 and 5, and day 8. Subjects will be interviewed to monitor for AEs and SAEs. Blood sampling for PK studies will be performed on days 8 and 10. In addition, prior to study drug administration on days 2-5, if subjects self-report any new signs or symptoms a targeted physical exam may be performed, if indicated, and the new signs or symptoms will be recorded as an AE or SAE as appropriate.

Following blood sampling performed on each day of dosing, 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 10 for groups 1-3 and Day 14 for group 4).

In the food effects evaluation, 12 subjects will be enrolled into the single dose cross over group. Group 4 can be enrolled concurrently with groups 1, 2, and 3. In group 4, half of the subjects will receive a single dose of 3 mg/kg of oxfendazole following an 8 hour fast and the other half will receive a single dose following a high fat meal. Each subject will be followed with safety laboratories, EKGs and PK studies for 7 days at which time they will cross over to receive a single dose of oxfendazole (3mg/kg) following either a high fat meal or following an 8 hour fast.

Individuals will be followed for 7 days after this second dose. During the food effects evaluation, each subject will receive study drug following a fast or a high fat meal. This will allow direct comparison for an individual as to the effect of food on the PK parameters of the study drug. Individuals will have EKG studies will be performed at screening, and two hours after dosing on days 1 and 8. Safety laboratories will be performed on day 1, 4 and 14. Blood sampling for PK studies will be performed (pre-dose and 30 minutes, 1, 2, 3, 4, 6, 9, 12 and 24 hours following each dose and on day 14).

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 10-14 day 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 12 months to finish the study.

4.1 **Substudies (if applicable)**

No substudies are planned

5 STUDY ENROLLMENT AND WITHDRAWAL

Up to 36 males and nonpregnant females, 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 12 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.

5.1 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 nonpregnant females between the ages of 18 and 45 years, inclusive.

2. Women of childbearing potential* must agree to practice adequate contraception** for the 28-day period before Day 0 through 4 months after the last dose of study medication.

** A woman is considered of childbearing potential unless surgically sterile (tubal ligation, bilateral oophorectomy, or hysterectomy) or post-menopausal (≥1 year).*

***Acceptable birth control methods include but are not limited to: abstinence from sexual intercourse with men; monogamous relationship with a vasectomized partner; double-barrier methods (condoms, diaphragms, spermicides); intrauterine devices; and licensed hormonal methods.*

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

2. *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. Acceptable screening laboratories*

   *Hemoglobin, white blood cell (WBC) count, neutrophil, and platelet counts, INR and PTT within normal ranges. AST < 44 and ALT < 44 and total bilirubin, creatinine must be equal to or below the upper limit of normal (creatinine 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.

3. Male participants must be willing to ensure use of condoms and spermicides for 4 months after the last dose of study medication.

4. Provide written informed consent before initiation of any study procedures.

5. Willing to be available for all study-required procedures, and visits for the duration of the study.

6. Individuals must agree to abstain from drug or alcohol use for 48 hours prior to enrollment through day 10 or 14.

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.

5.2 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. Pregnant women, women who are planning to become pregnant in the next 4 months, or women who are breastfeeding.

2. Body temperature ≥100.4°F (≥38.0°C) or acute illness within 3 days before administration of study drug (subject may be rescheduled).

3. 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.

4. 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 6.6 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 6.6 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.

5. Has history of sensitivity to related benzimidazole compounds (e.g., albendazole, mebendazole).
6. A diagnosis of schizophrenia, bipolar disease, or history of hospitalization for a psychiatric condition or previous suicide attempt.
7. 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.
8. Received an experimental agent* within 1 month before administration of study drug or expect to receive an experimental agent during the 10 or 14-day study period.

   *Vaccine, drug, biologic, device, blood product, or medication.
9. Any condition that would, in the opinion of the investigator, interfere with the study.*

   *This includes any condition that would 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.
10. A history of heavy alcohol* or illicit drug use†, or history of substance abuse#.

    *On average, 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.
11. 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 10 or 14.

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 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 protocol. 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.

5.3 Treatment Assignment Procedures

5.3.1 Enrollment and Randomization Procedures

Per International Conference on Harmonisation (ICH) guideline E6: Good Clinical Practice (GCP), screening records will be kept at the participating site to document the reason why an individual was screened, but failed trial entry criteria. The reasons why individuals failed screening will be recorded in the SDCC's AdvantageEDC^{SM} (Electronic Data Capture system).

Once consented, the subject will be enrolled by entry of demographic data and confirmation of eligibility for the trial. This is an open label study and subjects will be enrolled sequentially into groups 1, 2, 3 and 4 until each group has been completely enrolled. Enrollment of subjects will be done online using the enrollment module of AdvantageEDC^{SM}. AdvantageEDC^{SM} will generate a treatment number for each subject after the demographic and eligibility data have been entered into the system.

All participants in group 4 will receive oxfendazole in two conditions: after a high-fat breakfast and after fasting (separated by one week). The order of conditions will be randomly assigned upon enrollment in a 1:1 ratio. The randomization code will be prepared by statisticians at the SDCC and included in the enrollment module for the trial. When the subject is randomized and enrolled, AdvantageEDC^{SM} will generate a treatment assignment number.

Instructions for use of the enrollment module are included in the AdvantageEDC^{SM} User's Guide. Manual back-up procedures and instructions are provided for use in the event that the site temporarily loses access to the Internet or the online enrollment system is unavailable.

5.3.2 Masking Procedures

There is no masking planned for this study.

5.4 Withdrawal

5.4.1 Reasons for Withdrawal and Discontinuation of Study Product Administration

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 7.8 for procedures to be followed if a subject withdraws from the study.

For the multiple ascending dose groups, if the subject develops a study drug related SAE or grade 3 AE or laboratory abnormality during the five days of study drug administration, study drug will be discontinued though the subject will continue with safety monitoring through the completion of the study. If the subject in the food effect study develops a study drug related SAE or grade 3 AE or laboratory abnormality during the seven days following the first dose of the study drug, they will be discontinued from receiving the second dose of study drug, though the subject will continue with safety monitoring through the completion of the study.

5.4.2 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 7.8. 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 3 or more doses of study drug will not be replaced. If the subject has only received two or fewer doses of study drug prior to termination from the study, the subject will be replaced. If a subject vomits more than two doses (i.e. if vomiting occurs within 1 hour of study drug administration and the subject vomits on two days or more), the subject will be replaced. Additionally, if the subject vomits within 1 hour after the receipt of the dose on day 1, the subject will be replaced. No more than two subjects will be replaced in any group. 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 enrollment but before receipt of study product may be replaced. If a subject in Group 4 is lost to follow up after the first dose, the subject will be replaced.

5.5 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

6 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1 Study Product Description

Oxfendazole, methyl-5 (6)-phenylsulfiyl-2-benzimidazole carbamate, is a broad spectrum benzimidazole antihelminthic. It is the sulphoxide metabolite of fenbendazole. Oxfendazole is marketed for cattle in the United States as SYNANTHIC®.

6.1.1 Acquisition

Study product (Synanthic ® suspension) will be purchased through a commercial supplier.

Upon request by DMID, the investigational product will be shipped to the following address:

DMID-Clinical Agents Repository (CAR)
Fisher BioServices
20439 Seneca Meadows Parkway
Germantown, MD 20876
Tel: (240) 477-1350
Fax: (240) 477-1360
Email: DMID.CAR@ThermoFisher.com

6.1.2 Study product (Synanthic ® suspension) will be shipped from the DMID CAR to the study site upon request and approval by DMID. Formulation, Packaging, and Labeling

Oxfendazole is formulated as a white to grey powder; insoluble in water, slightly soluble in acetone, chloroform, ether, and methanol. The study product will be supplied as the commercial veterinary product Synanthic ®, which consists of an aqueous suspension in the following strength: 225 mg/mL (5).

6.1.3 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.

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

6.2.1 Dosage

Oxfendazole

In Groups 1-3, subjects will receive a total of five oral doses (3 mg/kg, 7.5 mg/kg or 15mg/kg), given daily for 5 days (Study Days 1-5). In Group 4, subjects will receive a total of two oral doses of 3 mg/kg, given on Study Days 1 and 8.

6.2.2 Preparation

The site Research Pharmacist will prepare study products for dispensing to the subject.

Additional details regarding subsequent labeling, and procedures for dispensing or administration of study product will be described in the protocol-specific MOP.

6.2.3 Administration

All study product will be orally administered vial oral dosing syringe(s).

6.3 Modification of Study Intervention/Investigational Product for a Participant

No modifications of study product dosing are planned at this time.

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

After receipt of study products, the site Principal Investigator (PI) is responsible for distribution and disposition of the study product, and has ultimate responsibility for study product accountability. The site PI may delegate this responsibility to the site pharmacist (or designee). The site pharmacist (or designee) must maintain study product records and document logs of receipt, accountability, and storage temperature conditions. These study product accountability and dispensing logs must be maintained in the study file. Upon completion of the study and after the final monitoring visit, unused study product will be retained until monitored and released for disposition, as applicable. Final disposition of the unused study product will be determined by DMID and communicated by the DMID Clinical Project Manager.

6.5 Assessment of Subject Compliance with Study Intervention/Investigational Product

Oral intake of the study product by the subject will be observed by study personnel. Subjects will be provided the dose in an oral dosing syringe. Immediately following administration of the dosethe subject will drink 100 mL of water to assure the entire dose is ingested. If vomiting occurs on the day of dosing and occurs at any time following ingestion of the study product, the dose for that day will not be replaced and subject will continue to be followed for safety and pharmacokinetic analyses.

6.6 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. If a prescription is authorized by their primary care provider or other licensed medical provider, we will counsel them to discuss the medication with the study team prior to starting the medication. One of the licensed clinical providers from the study team will help determine whether the prescription medication can be postponed until the study is completed. 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 the last day of the study visit schedule. 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.

7 STUDY SCHEDULE

7.1 Screening (Day -28 to -1): Clinic Visit 00

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

Assessment of Eligibility Criteria including:

Medical History. A complete medical history will be obtained by interview of the subjects. 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 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.
- 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 count, platelet count.
- **Coagulation Studies:** INR and partial thromboplastin time (PTT)
- **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
- **Urine pregnancy test**: for females of childbearing potential.

EKG. Perform 12 lead 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 10 or 14.
- Abstain from tobacco use from the time of screening through Day 10 or 14.
- Fasting (water is permitted) 8 or more hours prior to receipt of study product (except subjects in the fourth group who are to receive study product following a high fat meal.

These subjects will be provided breakfast in the Clinical Research Unit prior to receipt of the study product)

- Counseling on avoidance of pregnancy.

7.2 Enrollment/Baseline - GROUPS 1, 2 and 3

Clinic Visit 01, Day 1

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 and laboratory results obtained at the screening visit, Day 00).
- 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.
- Perform a urine pregnancy test for female subjects of childbearing potential.
- A heparin lock will be inserted, blood will be drawn (10 mL) for baseline PK (prior to product administration), and (15 mL) for safety labs (hemoglobin, white blood cell count, including neutrophil count, platelet count, INR, partial thromboplastin time, creatinine, Na, K, CL, CO_2, blood urea nitrogen, ALT, AST, and total bilirubin.
- Collect urine for dipstick testing for protein and glucose
- Enter subject into electronic data entry system.

Administration of Study Medication

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

- Subjects will remain fasting (water is permitted) for two hours after the administration of drug.
- 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 level will be drawn predose and at 30 minutes, 1, 2, 3, 4, 6, 9, and 12 hours (all times have a window of +/- 15 minutes except the 9 and 12 hour samples which have a window of +/- 30 minutes- it is critical to record the exact time of blood draw).
- Obtain EKG 2 hr after study drug administration (+/- 20 minutes)
- Assess AEs and SAEs throughout the day and prior to discharge from the CRU.
- Counsel on need to avoid alcohol, drugs, tobacco and medications throughout the study.
- Counseling on avoidance of pregnancy.
- Ask subject to remain fasting (water is permitted) for 8 hours prior to returning to the clinic in the morning.

7.3 Follow-up – GROUPS 1, 2 and 3

Clinic Visit 2, Day 2

- Vital signs including oral temperature, blood pressure, and pulse will be obtained.
- Review inclusion/exclusion criteria (including assessment of time of last oral food intake).
- A targeted physical exam may be performed, if indicated.
- Review concomitant medications
- Review for AEs and SAEs
- Draw 10 mL of blood for oxfendazole level prior to study drug administration - approximately 24 hours after dosing on day 1 (+/- 4 hours)

Administration of Study Medication

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

- Subjects will remain fasting (water is permitted) for two hours after the administration of drug.
- Obtain 10 mL of blood 2 hr after study drug administration (+/- 20 minutes) for oxfendazole level.
- Counsel on need to avoid alcohol, drugs, tobacco and medications throughout the study.
- Ask subject to remain fasting (water is permitted) for 8 hours prior to returning to the clinic in the morning.

Clinic Visit 03, Day 3

- Vital signs including oral temperature, blood pressure, and pulse will be obtained.
- Review inclusion/exclusion criteria (including assessment of time of last oral food intake).
- A targeted physical exam may be performed, if indicated.
- Review concomitant medications
- Review for AEs and SAEs
- Draw 10 mL of blood for oxfendazole levels prior to study drug administration - approximately 24 hours after dosing on day 2 (+/- 2 hours)
- Collect 15 mL of blood for safety panels (hemoglobin, white blood cell count, including neutrophil count, platelet count, INR, partial thromboplastin time, Na, K, Cl, CO_2, blood urea nitrogen, creatinine, ALT, AST, and total bilirubin).
- Collect urine for dipstick testing for protein and glucose.

Administration of Study Medication

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

- Subjects will remain fasting (water is permitted) for two hours after the administration of drug.
- Obtain EKG 2 hr after study drug administration (+/- 20 minutes)
- Obtain 10 mL of blood 2 hr after study drug administration (+/- 20 minutes) for oxfendazole levels
- Counsel on need to avoid alcohol, drugs, tobacco and medications throughout the study.
- Ask subject to remain fasting (water is permitted) for 8 hours prior to returning to the clinic in the morning.

Clinic Visit 04, Day 4

- Vital signs including oral temperature, blood pressure, and pulse will be obtained.
- Review inclusion/exclusion criteria (including assessment of time of last oral food intake).
- A targeted physical exam may be performed, if indicated.
- Review concomitant medications
- Review for AEs and SAEs
- Collect 10 mL of blood for oxfendazole level approximately 24 hours following dosing on day 3 (+/- 2 hours).

Administration of Study Medication

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

- Subjects will remain fasting (water is permitted) for two hours after the administration of drug.
- Obtain 10 mL of blood 2 hr after study drug administration (+/- 20 minutes) for oxfendazole levels
- Counsel on need to avoid alcohol, drugs, tobacco and medications throughout the study.
- Ask subject to remain fasting (water is permitted) for 8 hours prior to returning to the clinic in the morning.

Clinic Visit 05, Day 5:

- Vital signs including oral temperature, blood pressure, and pulse will be obtained.
- Review inclusion/exclusion criteria (including assessment of time of last oral food intake).
- A targeted physical exam may be performed, if indicated.
- Review concomitant medications
- Review for AEs and SAEs
- A heparin lock will be inserted, blood will be drawn (10 mL) for oxfendazole levels prior to study drug administration -approximately 24 hours after dosing on day 4 (+/- 2 hours)

- Collect 15 mL of blood for safety panels (hemoglobin, white blood cell count, including neutrophil count, platelet count, INR, partial thromboplastin time, Na, K, Cl, CO_2, blood urea nitrogen, creatinine, ALT, AST, and total bilirubin).
- Collect urine for dipstick testing for protein and glucose.

Administration of Study Medication

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

- Subjects will remain fasting (water is permitted) for two hours after the administration of drug.
- 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 level will be drawn predose and at 30 minutes, 1, 2, 3, 4, 6, 9, and 12 hours (all times have a window of +/- 15 minutes except the 9 and 12 hour samples which have a window of +/- 30 minutes- it is critical to record the exact time of blood draw).
- Obtain EKG 2 hr after study drug administration (+/- 20 minutes)
- Assess AEs and SAEs throughout the day and prior to discharge from the CRU.
- Counsel on need to avoid alcohol, drugs, tobacco and medications throughout the study.
- Counseling on avoidance of pregnancy.
- Ask subject to remain fasting (water is permitted) for 8 hours prior to returning to the clinic in the morning.

Clinic Visit 06, Day 6

- Vital signs including oral temperature, blood pressure, and pulse will be obtained.
- A targeted physical exam will 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 level approximately 24 hours after dosing on day 5 (+6 hours)

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 level
- Collect 15 mL of blood for safety panels (hemoglobin, white blood cell count, including neutrophil count, platelet count, INR, partial thromboplastin time, Na, K, Cl, CO_2, blood urea nitrogen, creatinine, ALT, AST, and total bilirubin).

- Collect urine for dipstick testing for protein and glucose.
- An EKG will be performed and will be reviewed by a cardiologist.

7.4 Final Study Visit 08 – Day 10 (+/- 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 level.
- Collect 15 mL of blood for safety panels (hemoglobin, white blood cell count, including neutrophil count, platelet count, INR, partial thromboplastin time, Na, K, Cl, CO_2, blood urea nitrogen, creatinine, ALT, AST, and total bilirubin).
- Collect urine for dipstick testing for protein and glucose.
- Counseling on avoidance of pregnancy.

7.5 Enrollment/Baseline- GROUP 4

Clinic Visit 01, Day 1

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 and laboratory results obtained at the screening visit, Day 00).
- Randomize to either fasting (water is permitted) or fed using the IDES system
- Review concomitant medications including confirmation of absence of medications in the past 48 hours.
- 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.
- Perform a urine pregnancy test for females of childbearing potential.
- A heparin lock will be inserted, blood will be drawn (10 mL) for baseline PK (prior to product administration), and (15 mL) for safety labs (hemoglobin, white blood cell count, including neutrophil count, platelet count, INR, partial thromboplastin time, creatinine, Na, K, CL, CO_2, blood urea nitrogen, ALT, AST, and total bilirubin).
- Collect urine for dipstick testing for protein and glucose.
- For subjects randomized to receive a high fat meal during the first dose, provide high fat breakfast. For subjects randomized to receive the first dose following an 8 hour fast, proceed to next steps without providing food.

Administration of Study Medication

A study nurse will administer a single 3 mg/kg oral dose of oxfendazole to the subject.

- Fasting (water is permitted) subjects will remain fasting (water is permitted) for two hours after the administration of drug.
- Fed subjects will receive a high fat breakfast. Approximately 30 minutes (+/- 15 minutes) following completion of the meal, the study nurse will administer a single 3 mg/kg oral dose of oxfendazole.
- 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 level will be drawn at 30 minutes, 1, 2, 3, 4, 6, 9, and 12 hours (all times have a window of +/- 15 minutes except the 9 and 12 hour samples which have a window of +/- 30 minutes- it is critical to record the exact time of blood draw).
- Perform EKG approximately 2 hours following study drug (+/- 20 minutes)
- Assess AEs and SAEs throughout the day and prior to discharge from the CRU.
- Counsel on need to avoid alcohol, drugs, tobacco and medications throughout the study.
- Counseling on avoidance of pregnancy.

7.6 Follow-up – GROUP 4

Clinic Visit 02, 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
- Draw 10 mL of blood for oxfendazole level -approximately 24 hours after dosing on day 1 (+/- 4 hours)
- Counsel on need to avoid alcohol, drugs, tobacco and medications throughout the study.

Clinic Visit 03, 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
- Collect 15 mL of blood for safety panels (hemoglobin, white blood cell count, including neutrophil and eosinophil counts, platelet count, INR, partial thromboplastin time, Na, K, Cl, CO_2, blood urea nitrogen, creatinine, ALT, AST, and total bilirubin).
- Collect urine for dipstick testing for protein and glucose.
- Remind subjects to remain fasting (water is permitted) for 8 or more hours prior to study visit 04.

- Counsel on need to avoid alcohol, drugs, tobacco and medications throughout the study.

Clinic Visit 04, Day 8 (+/- 1 day)

- Vital signs including oral temperature, blood pressure, and pulse will be obtained.
- Review inclusion/exclusion criteria (including assessment of time of last oral food intake).
- Perform a urine pregnancy test for females of childbearing potential.
- A targeted physical exam may be performed, if indicated.
- Review concomitant medications
- Review for AEs and SAEs
- A heparin lock will be inserted, blood will be drawn (10 mL) for baseline PK (prior to product administration)

Administration of Study Medication

A study nurse will administer a single 3 mg/kg oral dose of oxfendazole to the subject.

- For subjects who fasted during the first day of study drug administration, provide high fat breakfast prior to study drug administration. Approximately 30 minutes (+/- 15 minutes) following completion of the meal, the study nurse will administer a single 3 mg/kg oral dose of oxfendazole.
- For subjects who received a meal prior to the first day of study drug administration, subjects should fast for 8 hours prior to receipt of study drug and remain fasting (water is permitted) for two hours after the administration of drug.
- 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 level will be drawn at 30 minutes, 1, 2, 3, 4, 6, 9, and 12 hours (all times have a window of +/- 15 minutes except the 9 and 12 hour samples which have a window of +/- 30 minutes- it is critical to record the exact time of blood draw).
- Perform EKG approximately 2 hours following study drug (+/- 20 minutes)
- Assess AEs and SAEs throughout the day and prior to discharge from the CRU.
- Counsel on need to avoid alcohol, drugs, tobacco and medications throughout the study.
- Counseling on avoidance of pregnancy.

Clinic Visit 05, Day 9: (or 1 day following second dose)

- 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

- Draw 10 mL of blood for oxfendazole level -approximately 24 hours after dosing on day 8 (+/- 2 hours)
- Counsel on need to avoid alcohol, drugs, tobacco and medications throughout the study.

7.7 Final Study Visit 06 Day 14 (+/- 2 days) - GROUP 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
- Draw 10 mL of blood for oxfendazole level
- Collect 15 mL of blood for safety panels (hemoglobin, white blood cell count, including neutrophil count, platelet count, INR, partial thromboplastin time, Na, K, Cl, CO_2, blood urea nitrogen, creatinine, ALT, AST, and total bilirubin).
- Collect urine for dipstick testing for protein and glucose.
- Counseling on avoidance of pregnancy.

7.8 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
- Vital signs including oral temperature, blood pressure, and pulse will be obtained.
- Blood and urine will be collected for safety laboratory tests
- Blood 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.

7.9 Unscheduled Visit

Unscheduled visits may occur at any time during the study. Unscheduled visits may occur after the scheduled final study visit (Day 10 or 14, depending on Study Group) 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.

8 STUDY PROCEDURES/EVALUATIONS

8.1 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.

Interim Medical History: Will be obtained by interview of the subjects. Subjects will be queried regarding new signs or symptoms that have occurred since the screening medical history was obtained.

Concomitant Medications: All current medications and medications taken in the 30 days before the screening visit (prescription and over-the-counter drugs) will be documented, as well as vitamins and supplements, and alternative/complementary medications through the last study visit. 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 1 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 scheduled study visit and at the Early Termination Visit. Vital signs will be collected if indicated at the unscheduled 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. Please see section 9.2.1 and 9.2.2.

8.2 Laboratory Evaluations

8.2.1 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, neutrophil count, platelets

Coagulation includes: INR and partial thromboplastin time

Clinical chemistry includes: Na, K, Cl, CO_2, blood urea nitrogen, creatinine, ALT, AST, total bilirubin

Serology: HIV 1/2 antibody, hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV) antibody

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 may be deferred if a participant is menstruating, but should be performed as soon as possible.

Urine Pregnancy Test: will be performed at screening and Day 1 in females of child bearing potential for all groups.

EKG: will be performed in the research clinic by research personnel trained in EKG administration. EKG tracings will be interpreted by a board certified cardiologist.

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.

8.2.2 Special Assays or Procedures

Oxfendazole drug concentrations will be performed by Dr. Guohua An lab at the University of Iowa.

Blood samples for PK analysis will be collected in tubes containing sodium heparin as the anticoagulant at baseline. 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. Plasma samples will be shipped to the analytical lab frozen. Validated methods will be used to assay the oxfendazole concentration in each sample.

8.2.3 Specimen Preparation, Handling, Storage, and Shipping

8.2.3.1 Instructions for Specimen Preparation, Handling, Storage, and Shipping

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

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

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

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

9.2.1 Adverse Events

Adverse Event:

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 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 local and systemic reactions not meeting the criteria for “serious adverse events” should be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician’s assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis, which would include MD, PA, Nurse Practitioner, DO, or DDS), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the patient is screened should be considered as baseline and not reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

All AEs must be graded for severity and relationship to study product.

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

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

Grade 1: Mild: events require minimal or no treatment and do not interfere with the patient's daily activities.

Grade 2: Moderate: events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

Grade 3: Severe: events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

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

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

- Related – There is a reasonable possibility that the study product caused the 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.

9.2.2 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 patient or 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 patient or 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:

- recorded on the appropriate SAE CRF
- followed through resolution by a study clinician
- reviewed and evaluated by a study clinician

9.2.3 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. All clinically significant EKG abnormalities will be reported as an AE.

AE/SAEs, abnormal clinical laboratory test values or clinically significant EKG changes, or abnormal clinical findings will be documented, reported, and followed until the event has resolved or has stabilized.

If baseline clinical labs fall within Grade 1 parameters, then an AE is reported only if the value changes such that it falls into Grade 2 or higher at subsequent visits. For laboratory results that are abnormal according to the local laboratory reference range, but not considered a Grade 1 abnormality, these will not be considered AEs and will thus not be graded, but will be followed-up clinically at the discretion of the study site physician.

9.3 Reporting Procedures

AEs will be documented from the time of receipt of study drug on Day 1 (Visit 02) through the final study visit (approximately 10 or 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 the final study visit.

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

9.3.1 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 20817, 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.

9.3.2 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.

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

N/A.

9.3.4 Other Adverse Events (if applicable)

N/A

9.3.5 Reporting of Pregnancy

Pregnancies occurring in study subjects will be reported in IDES. No further study medication will be administered to pregnant subjects, but all study-mandated blood samples will be obtained and the subject will continue in follow-up for safety events. Pregnancies will be followed to pregnancy outcome pending the subject’s permission.

9.4 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.

9.5 Halting Rules

9.5.1 Sentinel Subject Halting Rules

For each of the multiple dose ascending groups (Groups 1-3), one sentinel subject will be dosed and monitored for 7 days after receiving the first dose of study product. If there are no

predefined safety events, a second sentinel subject will be enrolled and followed for a total of 7 days. If none of the sentinel subjects' halting criteria are met:

- any study drug related SAE
- any study drug related grade 3 AE or laboratory abnormality
- any two Grade 2 AE or laboratory abnormalities of the same laboratory parameter that are study drug related

then the remaining subjects in each group may be enrolled.

9.5.2 Dose Escalation Halting Criteria

Prior to dose escalation to the next cohort, the Statistical and Data Coordinating Center (SDCC) will notify the study PIs, DMID medical monitor (MM), and DMID Independent Safety Monitor (ISM) whether the below dose escalation criterion were met. Following enrollment and 10 days of safety follow up of the eight subjects in the dose group.

Dose escalation will not proceed if any of the following dose escalation criteria occur:

- any study drug related SAE
- any study drug related grade 3 AE or laboratory abnormality
- any two Grade 2 AE or laboratory abnormalities of the same laboratory parameter

In addition to these criteria, dose escalation may also stop for other reasons per the advice of the SMC, ISM, or DMID Medical Monitor for further evaluation, discussion, and recommendations from the SMC.

If the above dose escalation halting criteria are NOT met, the dose escalation may proceed with agreement of DMID.

9.5.3 Study Halting Rules

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 one day after administration of study product.

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

- Two or more subjects experience generalized urticaria within three days 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.

- Two or more subjects develop new QTc prolongation on EKG that are deemed clinically significant by a reviewing cardiologist.

- Two or more subjects develop grade 3 laboratory abnormalities deemed related to the study drug.

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.

9.5.4 **Individual Halting Rules**

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

- Subject experiences a study drug-related Stevens Johnson Syndrome.

- Subject experience generalized urticaria within 72 hours after administration of study product.

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

- Subject develops new QTc prolongation on EKG that are deemed clinically significant by a reviewing cardiologist.

- Subject develops any grade 3 laboratory abnormalities deemed related to the study drug.

- Subject develops any grade 3 AE deemed related to the study drug.

9.6 **Safety Oversight (ISM plus SMC)**

Safety oversight will be under the direction of an SMC. The SMC will have a formal meeting after the third study group has completed the day 10 study visit. The SMC will review available safety data for Groups 1-3, after the third study group has completed the day 10 study visit. This meeting will be scheduled expeditiously.. If halting rules are identified, more frequent

meetings may be held. The SMC will operate under the rules of a DMID-approved charter that will be written at the organizational meeting of the SMC. At this time, each data element that the SMC needs to assess will be clearly defined. The SMC will advise DMID of its findings.

9.6.1 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.

9.6.2 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 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. 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. The SMC will have access to unblinded data during its closed session.

The SMC will review and discuss safety data at the following milestones:

- The SMC will review available safety data for Groups 1-3, after the third study group has completed the day 10 study visit. Ad hoc review: may be in response to an anticipated safety issue such as a dose escalation or study halting rule being met.

- Final review meeting: 6 to 8 months after clinical database lock to review the cumulative unblinded safety data for the study. The data will be provided in a standard summary format. The SMC may be asked to provide recommendations in response to questions posed by DMID.

10 CLINICAL MONITORING

10.1 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.

11 STATISTICAL CONSIDERATIONS

This is an open-label Phase I study to assess the safety and pharmacokinetics of oxfendazole in healthy males and nonpregnant females, ages 18-45. The primary objectives are to assess the safety of oxfendazole administered daily for five days and to assess the safety of oxfendazole administered as a single dose with or without food. The secondary objectives are to define the multi-dose kinetics of oxfendazole and to determine the effect of food on the kinetics of oxfendazole.

Primary endpoints:

1. The rate of adverse events (AEs) related to oxfendazole within 10 days of receipt of oxfendazole given for 5 sequential, daily oral doses of either 3, 7.5 or 15 mg/kg

2. The rate of adverse events (AEs) related to oxfendazole within 7 days of receipt of oxfendazole given as a single daily dose either following an 8 hour fast or following a high fat meal.

Secondary endpoints:

1. Plasma Cmax, Tmax, AUC, $T_{1/2}$ of oxfendazole at specified time points following each dose of a 5 day daily regimen of either 3, 7.5 or 15 mg/kg

2. Plasma Cmax, Tmax, AUC, $T_{1/2}$ of oxfendazole at specified time points following a single dose of oxfendazole administered after an 8 hour fast or after a high fat meal.

11.1 Study Hypotheses

The primary objective of this study will be assessed through estimation rather than hypothesis testing, as this is a Phase I study with small sample sizes. The study includes eight subjects in each of the first three cohorts and twelve subjects in the fourth cohort.

The secondary objective of defining the multi-dose kinetics of oxfendazole will be assessed using a descriptive analysis with no formal hypothesis test. For the secondary objective of the determination of the effect of food on the kinetics of oxfendazole, equivalence between the fasting (water is permitted) and fed conditions will be tested using 90% confidence intervals and 80-125% equivalence limits for $AUC_{0-\infty}$, AUC_{0-24}, and C_{max} in accordance with FDA guidance. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126833.pdf

11.2 Sample Size Considerations

The sample sizes were selected to obtain preliminary safety information on a small cohort of subjects before proceeding to larger trials. In this Phase 1 study, we are concerned with rates of adverse events, which theoretically could occur due to oxfendazole treatment. The dosing regimens with respective sample sizes are described in Table 4 below:

Table 4. Sample sizes for each dose regimen

Cohort	Dose Regimen	Sample size
1	3 mg/kg daily for 5 days	8
2	7.5 mg/kg daily for 5 days	8
3	15 mg/kg daily for 5 days	8
4	Single dose of 3 mg/kg after fasting (water is permitted) with cross-over to single dose of 3 mg/kg after high-fat meal.	12

The study will produce preliminary estimates of adverse event rates for each dosing regimen. The true adverse event rates within each dosing regimen are unknown. The below table displays probabilities of observing at least one adverse event within a cohort assuming different true underlying event rates and sample sizes. For example, if an adverse event has a true rate of 0.20, then the probability of observing at least one adverse event among 8 subjects is 0.83. There is a 0.93 probability of observing the event among 12 subjects. The probabilities were calculated using R statistical software, version 3.2.2.

Table 5. Probabilities of observing adverse events for various event rates and sample sizes

	Probability of observing at least one adverse event within a cohort	
True Rate of Adverse Event	Among 8 subjects	Among 12 subjects
0.01	0.08	0.11
0.05	0.34	0.46
0.08	0.49	0.63
0.10	0.57	0.72
0.15	0.73	0.86
0.20	0.83	0.93

With 12 total participants to assess the secondary objective of the determination of the effect of food on the kinetics of oxfendazole, the power is 80% when the coefficient of variation is less than 0.175 and 64% when the coefficient of variation is 0.2.

11.3 Planned Interim Analyses (if applicable)

No interim analyses are planned.

11.3.1 Safety Review

The SMC will have a formal meeting after all subjects in groups 1-3 have completed the day 10 study visit. This meeting will be scheduled expeditiously, but this SMC review is not required prior to enrollment into study group 4. This report will summarize adverse events as described in section 11.4.3 below. Additional safety review may occur if halting rules are met.

11.4 Final Analysis Plan

The final analysis will be performed and clinical study report completed when all primary and secondary endpoint data are available. This study, like other Phase 1 studies, is exploratory rather than confirmatory; its purpose is to estimate adverse event rates and characterize pharmacokinetic profiles than to test formal statistical hypotheses. Estimates will be presented with their 95% confidence intervals. Results will be presented in tabular format, as well as graphically when appropriate.

11.4.1 Populations for Analysis

Safety Population

All participants who receive study drug and for whom any safety data are available will be included in the safety population.

PK Analysis Population

All participants who receive study drug and have at least one evaluable PK concentration will be eligible for the PK analysis population.

11.4.2 Analysis of Demographics

Demographic characteristics (age, gender, race, ethnicity) of each cohort will be summarized numerically.

11.4.3 **Analysis of Safety**

Adverse experiences (spontaneous reports) will be coded into MedDRA® preferred terms. The number of subjects experiencing unsolicited adverse events and the number of spontaneous events, classified using MedDRA® System Organ Classes and Preferred Terms, reported throughout the study after treatment administration will be tabulated by cohort. The severity and relationship to study product of the unsolicited adverse events will also be assessed. Serious adverse events will be described. A complete listing of adverse experiences for each subject will provide details including severity, relationship to treatment, onset, duration, and outcome. Solicited clinical laboratory results and vital signs will be graded and summarized by cohort and study day.

11.4.4 **Pharmacokinetic Analysis**

PK parameters for oxfendazole will be calculated using non-compartmental analysis. Parameters will be summarized separately by group and dose.

Maximum concentration (C_{max}), time of maximum concentration (T_{max}), and the pre-dose trough concentrations (C_{trough}) will be directly estimated from the observed concentration-time curve. Area under the curve (AUC) will be calculated using the linear up-log down trapezoidal method. 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 for λ_z to be estimable. Half-life ($t_{½}$) will be calculated as $\ln(2)/\lambda_z$.
In Groups 1-3, $AUC_{0-\tau}$ will be calculated as AUC to the end of the 24-hour dosing interval. Oral clearance at steady state will be calculated using $AUC_{0-\tau,ss}$ after the Day 5 (expected steady state) dose as

$$CL_{ss} / F = \frac{Dose}{AUC_{0-\tau,ss}}.$$

The observed accumulation ratio (AR) following multiple dosing will be estimated using the ratio of $AUC_{0-\tau}$ following multiple and single dosing. When λ_z is estimable, AR will also be estimated using λ_z calculated following multiple dosing:

$$AR = \frac{1}{1 - e^{-\lambda_Z \tau}}$$

The relationship between exposure (C_{max} and AUC) and dose, i.e., dose proportionality, will be examined using ANOVA or the power model

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

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

Group 4 parameters will be summarized by condition (fasting (water is permitted) or fed). In group 4, 90% confidence intervals for ratios of key exposure parameters will be estimated using appropriate analysis of variance (ANOVA) models on the log-transformed parameters. Key exposure parameters will be Cmax, AUC to the time of the last quantifiable concentration (AUC_{0-t}), and, when λ_z is estimable, AUC extrapolated to infinity ($AUC_{0-\infty}$).

Listings of individual subject plasma concentrations, actual blood sampling times, PK parameters, and graphs of concentration vs. time will be prepared by group. Parameter estimation using noncompartmental analysis will be done using appropriate computer software, such as Phoenix WinNonlin, as determined by the sponsor.

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Describe who will have access to records. As part of participating in a DMID-sponsored, DMID-affiliated, or manufacturer-sponsored study, each site will permit authorized representatives of the sponsor(s), DMID, and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' memory aid or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

13 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.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Ethical Standard

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

14.2 Institutional Review Board

Prior to 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 investigator and approved by DMID prior to submission to the IRB.

14.3 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. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study product. Consent forms will be IRB-approved and the subject will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. The subjects will sign the informed consent document prior to any procedures being done specifically for the study. The subjects should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

14.3.1 Informed Consent/Assent Process (in Case of a Minor)

Not applicable

14.4 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.

14.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests 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 study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

14.6 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.

14.7 Future Use of Stored Specimens

No specimens will be saved for future use. Once the study has been completed DMID will instruct the site and Fisher BioServices to destroy all residual samples. The destruction of residual samples will be appropriately documented.

15 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.

15.1 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.

15.2 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.

15.3 Types of Data

Data for this study will include safety, laboratory studies, EKG data and pharmacokinetic data for the study drug.

15.4 Timing/Reports

Safety data will be reviewed by the SMC per the SMC charter for this study. The SMC will review available safety data for Groups 1-3, after the third study group has completed the day 10 study visit. A second report will be generated approximately 6-8 months after study completion that will include all unblinded safety data for groups 1-4. Interim statistical reports may be generated as deemed necessary and appropriate by DMID.

15.5 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.

15.6 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.dmidcroms.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.

16 PUBLICATION POLICY

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

Groups 1,2 and 3

					Follow Up Visits							
		Screening Study Visit 00	Baseline Study visit 01	Study Visit 02	Study Visit 03	Study Visit 04	Study Visit 05	Study Visit 06	Study Visit 07	Study Completion Visit 08	Unscheduled Visit	Early Termination Visit
Study Day		D-28 to -1	D1	D2	D3	D4	D5	D6	D8	D10		
Visit Window		N/A	N/A	N/A	N/A	N/A	N/A	N/A	+/-1	+/-2		
Signed Consent Form		X										
Assessment of Eligibility Criteria		X	X	X	X	X	X					
Enrollment			X									
Review of Medical History		X	X								X	X
Review of Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X
Administration of Study Medication			X	x	X	X	X					
Physical Examination	Complete	X	X									
	Symptom-Directed			(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
	Vital Signs	X	X	X	X	X	X	X	X	X	(X)	X
Assessment of Adverse Events and SAEs			X	X	X	X	X	X	X	X	X	X
Clinical Laboratory	Chemistry	X	X		X		X		X	X		X
	Hematology	X	X		X		X		X	X		X
	Coagulation Studies	X	X		X		X		X	X		X
	Serology	X										
	Urinalysis	X	X		X		X		X	X		X
	Pregnancy Test	X	X									
Research Laboratory	PK studies 10 mL whole blood		X	X	X	X	X	X	X	X		X

Groups 1,2 and 3

		Screening Study Visit 00	Baseline Study visit 01	Study Visit 02	Study Visit 03	Study Visit 04	Study Visit 05	Study Visit 06	Study Visit 07	Study Completion Visit 08	Unscheduled Visit	Early Termination Visit
					Follow Up Visits							
Study Day		D-28 to -1	D1	D2	D3	D4	D5	D6	D8	D10		
Visit Window		N/A	N/A	N/A	N/A	N/A	N/A	N/A	+/-1	+/-2		
Other Procedures	EKG	X	X		X		X		X			

(X) – As indicated/appropriate.
Hematology – Hemoglobin, WBC and neutrophil count, platelet count.
Biochemistry – **Screening**: creatinine, ALT, AST, random glucose, total bilirubin.
– **Follow Up Visits**: creatinine, sodium, potassium, chloride, carbon dioxide, blood urea nitrogen ALT, AST, total bilirubin.
Coagulation Studies– INR, and partial thromboplastin time (PTT)
Serology – Hepatitis B surface antigen, hepatitis C antibody, human immunodeficiency virus (HIV)
Urinalysis – Urine Dipstick for protein and glucose
Research Laboratory – **Days 1 and 5**: 10 mL blood for baseline PK (prior to drug administration), 10 mL blood at 30 minutes,1, 2, 3, 4, 6, 9, and 12 hours (all times have a window of +/- 15 minutes except the 9 and 12 hour samples which have a window of +/- 30 minutes)
Day 2: 10 mL blood prior to study drug administration-approximately 24 hours after dosing on previous day (+/- 4 hours) and 2 hours after study drug administration (+/- 20 minutes)
Days 3 and 4: 10 mL blood prior to study drug administration-approximately 24 hours after dosing on previous day (+/- 2 hours)
Day 6: 10 mL blood-approximately 24 hours after dosing on previous day (+6hours)

Group 4

		Screening Study Visit 00	Baseline Study visit 01	Follow Up Visits: Study Visit 02	Study Visit 03	Study Visit 04	Study Visit 05	Study Completion Study Visit 06	Unscheduled Visit	Early Termination Visit
Study Day		D-28 to -1	D1	D2	D4	D8	D9	D14		
Visit Window		N/A	N/A	N/A	N/A	+/-1	N/A	+/-2		
Signed Consent Form		X								
Assessment of Eligibility Criteria		X	X			X				
Randomization/Enrollment			X							
Review of Medical History		X	X						X	X
Review of Concomitant Medications		X	X	X	X	X	X	X	X	X
Administration of Study Medication			X			X				
Physical Examination	Complete	X	X							
	Symptom-Directed			(X)	(X)	(X)	(X)	(X)	(X)	X
	Vital Signs	X	X	X	X	X	X	X	(X)	X
Assessment of Adverse Events and SAEs			X	X	X	X	X	X	X	X
Clinical Laboratory	Chemistry	X	X		X			X		X
	Hematology	X	X		X			X		X
	Coagulation Studies	X	X		X			X		X
	Serology	X								
	Urinalysis	X	X		X			X	(X)	X
	Pregnancy Test	X	X			X				
Research Laboratory	PK Studies 10 mL whole blood		X	X		X	X	X		X
Other Procedures	EKG	X	X			X				

(X) – As indicated/appropriate
Hematology – Hemoglobin, WBC and neutrophil count, platelet count.
Biochemistry – **Screening**: creatinine, ALT, AST, random glucose, total bilirubin.
– **Follow Up Visits**: creatinine, sodium, potassium, chloride, carbon dioxide, blood urea nitrogen ALT, AST, total bilirubin.
Coagulation Studies– INR and partial thromboplastin time (PTT)
Serology – Hepatitis B surface antigen, hepatitis C antibody, human immunodeficiency virus (HIV)
Urinalysis – Urine Dipstick for protein and glucose
Research Laboratory – **Days 1 and 8**: 10 mL blood for baseline PK (prior to drug administration), 10 mL blood at 30 minutes, 1, 2, 3, 4, 6, 9, and 12 hours (all times have a window of +/- 15 minutes except the 9 and 12 hour samples which have a window of +/- 30 minutes)
Day 2 and 9: 10 mL blood –approximately 24 hours following study drug dose (+/- 4 hours)

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	>102.0
** 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 3 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**

Arrhythmia		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 (water is permitted) – 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	5.5 – <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 $\geq$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
INR –(International Normalized Ratio of the prothrombin time)	1.3 to <1.7	1.8- <2.3	≥ 2.4
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
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	>499 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
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
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
INR	0.9-1.2	Same
Glucose (random)	<140	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