CLINICAL RESEARCH IN INFECTIOUS DISEASES

DMID Protocol 12-0053: ***A Randomized, Double-Blind Placebo-Controlled Phase I Trial Evaluating the Safety and Pharmacokinetics of Oxfendazole***

PK STATISTICAL ANALYSIS PLAN

Principal Investigator:

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Version 1.0

15 September 2015

Prepared and Distributed by:
Statistical and Data Coordinating Center (SDCC)
The EMMES Corporation
Rockville, Maryland USA

STATISTICAL ANALYSIS PLAN

Trial Number Code:	DMID Protocol: 12-0053
Development Phase:	Phase I
Product:	Oxfendazole suspension
Form/Route:	Tablet/Oral
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health 6610 Rockledge Drive Bethesda, Maryland 20892-6603
Principal Investigator:	Patricia Winokur, MD University of Iowa University of Iowa Hospitals and Clinics 200 Hawkins Drive Iowa City, IA 52242 Phone: 319-384-1735 Fax: 319-335-8318 E-mail: patricia-winokur@uiowa.edu
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STATISTICAL ANALYSIS PLAN – *(Continued)*

Biostatistician:	Tina J.T. Dube, PhD The Emmes Corporation 401 North Washington Street, Suite 700 Rockville, MD 20850 Email: tdube@emmes.com
Clinical Trial Initiation Date:	17 November 2014
Clinical Trial Completion Date:	October 2015 (Anticipated)
Date of the Analysis Plan:	15 September 2015
Version Number:	**Version 1.0**

PROTOCOL SYNOPSIS

Title of the Trial	A Randomized, Double-Blind Placebo-Controlled Phase I Trial Evaluating the Safety and Pharmacokinetics of Oxfendazole
Investigators	Patricia Winokur, MD University of Iowa University of Iowa Hospitals and Clinics 200 Hawkins Drive Iowa City, IA 52242 Phone: 319-384-1735 Fax: 319-335-8318 E-mail: patricia-winokur@uiowa.edu
Trial Center	The University of Iowa
Trial Period	First Subject First Visit: 17 November 2014 Last Subject Last Visit: October 2015 (anticipated)
Development Phase	Phase I
Objectives	**Primary:** • Assess the safety and tolerability of oxfendazole in healthy adults. **Secondary:** • Assess the pharmacokinetic profile of oxfendazole • Assess the metabolism of oxfendazole
Sample Size	70 (10 subjects in each of 7 dose groups)
Investigational product	Single oral dose of an aqueous suspension of oxfendazole, a benzimidazole carbamate antiparasitic drug.
Duration of Follow-up	2 weeks
Endpoints for Analysis	**Primary Endpoint** The rate of adverse events (AEs) related to oxfendazole within 14 days of receipt of a single oral dose. **Secondary Endpoints** Plasma Cmax, Tmax, AUC, $t_{1/2}$ of oxfendazole for each dosage group. Plasma and urine concentrations of oxfendazole fenbendazole and oxfendazole sulfone at time points specified in Appendix A Schedule of Events and described in Section 4 Study Design relative to oral dosing.

PHARMACOKINETIC ANALYSIS PLAN SIGNATURE PAGE:

Sponsor: Division of Microbiology and Diseases
National Institute of Allergy and Infectious Diseases
National Institutes of Health

Protocol Number: **DMID 12-0053**

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

Principal Investigator: Patricia Winokur, M.D.
Signed: _____ Date: _____

Title:

DMID Scientific Lead: Greg Deye, M.D.
Signed: _____ Date: _____

Title:

The Emmes Corporation: Tina J.T. Dube, Ph.D.
Signed: _____ Date: _____

Title: Statistician

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LISTING OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Concentration-Time Curve
AUC_{0-t}	Area Under the Curve to the Final Sample
$AUC_{0-\infty}$	AUC Extrapolated to Infinity
BQL	Below the Quantification Limit
C_{last}	Last measurable (non-zero) concentration
CL	Clearance
CL/F	Oral Clearance
CL_R	Renal Clearance
C_{max}	Maximum Plasma Concentration
CNS	Central Nervous System
CRF	Case Report Form
CSR	Clinical Study Report
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
eCRF	Electronic Case Report Form
EKG	Electrocardiogram
F	Bioavailability
FDA	Food and Drug Administration
f_e	Fraction Excreted Unchanged in Urine
f_u	Fraction Unbound in Plasma
GM	Geometric Mean
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
LLOQ	Lower Limit of Quantification
LLN	Lower Limit of Normal
MedDRA®	Medical Dictionary for Regulatory Activities

LISTINGS OF ABBREVIATIONS – *(Continued)*

MOP	Manual of Procedures
N	Number (typically refers to subjects)
NCA	Noncompartmental Analysis
NF	National Formulary
NEJM	New England Journal of Medicine
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
NOEL	No Observed Effect Level
OHRP	Office for Human Research Protections
OHSR	Office for Human Subjects Research
ORA	Office of Regulatory Affairs, DMID, NIAID, NIH, DHHS
OXF	Oxfendazole
PD	Pharmacodynamic
PG	Pharmacogenomic
PHI	Personal Health Information
PI	Principal Investigator
PK	Pharmacokinetics
PKAR	Pharmacokinetics Analysis Report
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 of 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

1 PREFACE

The Statistical Analysis Plan (SAP) for "DMID Protocol 12-0053: A Randomized, Double-Blind Placebo-Controlled Phase I Trial Evaluating the Safety and Pharmacokinetics of Oxfendazole" describes and expands upon the statistical information presented in the protocol.

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

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

Some minor modifications may be necessary to the planned design of tables, figures, and listings to accommodate data collected during the actual study conduct.

IMPORTANT NOTES:

Tables, indicated by footnote, presented in this statistical analysis plan will be presented by dose group.

This SAP relies on simulated (fake) sample data to illustrate the statistical methods, tables, and graphical displays that will be used in analyzing the study data. These simulated data are for illustrative purposes only and no inferences should be drawn regarding pharmacokinetic profiles. Appropriate scales and units will be added to all figures for the final analysis.

2 INTRODUCTION

With current treatment strategies for neurocysticercosis, cure is achieved in approximately 50% of patients despite multiple doses of drug. In animal studies, single oral doses of oxfendazole appear to have substantial activity against the tissue stages of Taenia solium. Oxfendazole, as a single dose, might be efficacious against neurocysticercosis in humans. A Phase I study is needed to evaluate its safety, metabolism, and pharmacokinetics (PK) in humans. As a result, this Phase I randomized, double-blind, placebo-controlled evaluation of the safety and PK of escalating single oral doses of oxfendazole (0.5, 1,

3, 7.5, 15, 30, 60 mg/kg) in healthy volunteers is designed to assess safety, metabolism and PK in humans.

2.1 Purpose of the Pharmacokinetic Analyses

The study is a rising dose safety/tolerance study in which plasma is collected for analysis of oxfendazole, fenbendazole and sulfone levels. The primary aim is to determine to what level single doses can be increased without causing limiting toxicity in normal volunteers.

The analyses described will assess the pharmacokinetics of a single dose of oxfendazole (0.5, 1, 3, 7.5, 15, 30, 60 mg/kg) in healthy volunteers and will be included in the Interim PK Analysis Report (PKAR) and also may be distributed in limited fashion such as for grant applications.

Subject level results will be included in the clinical study report (CSR). Dose group-level (mean and standard deviations) results will be presented at each interim look. This PK analysis plan describes the analyses that will be performed.

3 STUDY DESIGN, OBJECTIVES AND ENDPOINTS

3.1 Study Design

This Phase I study is a randomized, double-blind, placebo-controlled evaluation of the safety and PK of escalating single oral doses of oxfendazole (0.5, 1, 3, 7.5, 15, 30, 60 mg/kg) in healthy volunteers. Each cohort will comprise 10 volunteers (8 drug, 2 placebo). Subjects will be monitored for 2 weeks after dosing, including monitoring the PK and metabolism of oxfendazole in blood and urine. Projected duration of subject participation will be 3-6 weeks of face to face visits, including the screening period. It is anticipated that it will take 18 months to finish the study.

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

Sample Collection:

Blood and urine will be obtained for PK analysis. Blood samples for PK analysis are collected at 14 time points: baseline (prior to product administration); 1, 2, 4, 6, 8, 10, 12 (all times have a window of +/- 15 minutes except the 10 and 12 hour samples which have a window of +/- 30 minutes), and 24 (+8) hours; and Days 3, 4, 6, 8 and 15 after dosing. Urine for oxfendazole, metabolites, and creatinine will be

collected. Urine for PK analysis will be collected at baseline (prior to product administration) and for the first 24 hours after product administration with specific collections times of urine for oxfendazole, 0-4, 4-8, 8-12, 12-24. Spot urine samples will be collected at 24 (+ 8 hrs) and on Day 3 after dosing.

Samples for PK studies will be processed at Dr. Daryl Murry's laboratory at the University of Iowa.

3.2 Study Objectives (Pharmacokinetic Only)

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

3.3 Study Outcome Measures (Pharmacokinetic Only)

- Plasma Cmax, Tmax, AUC, $t_{1/2}$ of oxfendazole for each dosage group.
- Plasma and urine concentrations of oxfendazole fenbendazole and oxfendazole sulfone at the following time points:
  - Blood- prior to dosing for baseline PK data, and then at, 1, 2, 4, 6, 8, 10, 12, 24 (+ 8) hours, Day 3 and Day 15.
  - Urine- prior to dosing for baseline PK data, and then for the first 24 hours following the schedule of urine collections at 0-4, 4-8, 8-12, 12-24 hours. Spot urine samples will be collected on Days 2 and 3 following drug administration.

4 PHARMACOKINETIC ANALYSES

4.1 General Considerations

Subject characteristics will be summarized overall and by dose group. PK parameters determined by noncompartmental approaches will be summarized by dose group. Statistics include the arithmetic mean, geometric mean, standard deviation (SD), coefficient of variation (CV), minimum (min), maximum (max), and median.

4.2 PK Analysis Population

All subjects who receive active study drug and have at least 1 measured oxfendazole concentration at a scheduled PK time point after start of dosing are eligible for the PK population. If any subjects are found to be noncompliant with respect to dosing, have incomplete data, or an event that is likely to affect PK, a decision will be made on a case-by-case basis as to their inclusion in the population. Subjects excluded from the PK analyses and their reasons for exclusion will be denoted and detailed in the PKAR.

4.3 Demographics and Other Subject Characteristics

The following variables will be summarized for the PK analysis population:

- Demographic variables: gender, age, race, and ethnicity.
- Physical characteristics: height and weight recorded at the PK dosing visits or carried forward from a previous study visit.
- Clinical laboratory parameters: Creatinine, AST, ALT

4.4 Summary of Pharmacokinetic Sampling and Sample Properties

4.4.1 Handling of Special Cases in Analyses

Key protocol violations and deviations related to PK sample collection or storage that could potentially impact PK results will be summarized. Samples with bioanalytical errors reported by the laboratory will be excluded. Collection times of samples missing the actual collection time will be imputed using the nominal collection time. Such samples will be identified in the PKAR.

4.5 Interim Pharmacokinetic Analyses

This study is a rising dose safety/tolerance study in which plasma is collected for analysis of oxfendazole, fenbendazole and sulfone levels. The primary aim is to determine to what level single doses can be increased without causing limiting toxicity in normal volunteers.

In order to assess safety of rising dose levels and to facilitate planning for future product development activities without jeopardizing data integrity for this trial, pharmacokinetic data will be entered into the trial database as they become available and reviewed after each dose group. After PK data for a cohort is complete, locked and finalized, group-level results will be distributed to the study team. These data may be distributed in limited fashion such as grant applications.

Subject baseline characteristics will be summarized and presented by Dose group. Dose group-level summary statistics as well as line plots for of oxfendazole, fenbendazole and sulfone levels will be presented**.**

All PK parameters will be presented by group and specimen type. No individual subject summaries will be presented in interim pharmacokinetic report.

4.6 Primary Pharmacokinetic Analysis

4.6.1 Concentration Summaries

Dose group-level summary plots will be produced by plotting plasma concentrations (mean ± SD) versus nominal time to explore average trends and variability. Dose group-level summary plots of the amount excreted in urine will be produced by plotting the cumulative amount excreted in each collection interval versus the midpoint of the collection interval.

4.6.2 Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated using actual post-dose time. All PK parameters will also be summarized by dose group and specimen type using descriptive statistics. Additionally, subject-level PK parameters will be presented by subject in data listings in the final PKAR.

The following parameters will be calculated from the concentration-time profiles:

Maximum plasma concentration (C_{max}) is defined as: the maximum observed drug concentration in blood plasma for a particular dose interval.

Time of maximum plasma concentration (T_{max}) is defined as: the time at which the maximum plasma concentration occurs.

AUC_{0-t} is defined as: the area under the concentration-time curve from administration (time 0) to the time of the last quantifiable concentration at time =t.

The following parameters will be estimated when the elimination rate constant is estimable:

Elimination rate constant (λ_z) is defined as: the first-order rate constant describing rate of elimination from plasma.

Elimination half-life ($t_{1/2}$) is defined as: the time required for a drug concentration to be reduced by half during the elimination phase. The terminal half-life will be estimated by ln(2) divided by λ_z.

$AUC_{0-\infty}$ is defined as: the total area under the concentration-time curve and is computed by adding AUC_{0-t} to an extrapolated value equal to the last measured concentration greater than limits of quantitation divided by **λ_z** and will be calculated using

$$AUC_{0-\infty} = AUC_{0-t} + \frac{C_{tf}}{\lambda_Z},$$

where C_{tf} is the last measurable concentration ≥ LLOQ

Oral clearance (CL/F) is calculated as: the dose divided by the $AUC_{0-\infty}$.

Apparent volume of distribution (V_z/F) is defined as: the theoretical volume that the total amount of administered drug would occupy to provide the same concentration as it currently is in blood plasma divided by the bioavailability.

$$Vz / F = \frac{Dose}{\lambda z \times AUC_{0-\infty}}$$

Amount of drug excreted in urine (Ae) is defined as: the cumulative amount of drug excreted in urine. Ae will be used to calculate the fraction of dose excreted in urine (fe) and estimate renal clearance (CL_R).

Additional parameters may be estimated, if appropriate.

4.6.3 Pharmacokinetic Parameter Estimation

Samples with concentrations greater than the LLOQ will be considered for the estimation of λ_z. This slope will be computed from log-transformed concentration data. The correlation between time and concentration in the time points used to estimate λ_z should be sufficiently high ($|r|>0.8$) for λ_z. to be estimated reliably. At least three samples will be used for the calculation of λ_z. The observation collected at Tmax may be considered to be used in the calculation if the concentration at that time point is not strongly affected by drug absorption. The range of selected time points should be >1.5 half-lives.

Samples used to calculate λ_z along with the number of samples used for the calculation will be included in subject listings.

The AUC will be computed using the linear-up log-down (linear-log) trapezoidal method in WinNonlin (Pharsight Corporation, Cary, NC).

4.7 Additional Analyses

In order to assess dose proportionality and linearity across the range of administered doses, plots of dose versus exposure ($AUC_{0-\infty}$ or Cmax) will be presented with corresponding descriptive statistics such as R2. Parameter estimates for an appropriate (simple least squares, weighted least squares, or power) regression model will also be provided [2, 3]. Model selection will be guided by graphical diagnostics to assess model fit.

5 REPORTING CONVENTIONS

P-values ≥0.001 and ≤0.999 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001"; p-values greater than 0.999 will be reported as ">0.999". Parameters directly derived from source data (e.g., Cmax and Cmin) will be reported and analyzed with the same precision as the source data. Parameters derived from actual sample collection times (e.g., Tmax and Tmin) will be reported with the same precision as the actual elapsed sampling time value of the source data. The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles such as the minimum and maximum will use the same number of decimal places as the original data. Proportions will be presented as two decimal places; proportions <0.01 will be presented as "<0.01". Percentages will be reported to the nearest whole number; values < 1% will be presented as "<1". Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

6 TECHNICAL DETAILS

Estimation of pharmacokinetic parameters will be performed in a validated version of WinNonlin version 6.3 or later, or a similar software package. WinNonlin or SAS version 9.3 or later will be used to generate all tables, figures, and listings

7 REFERENCES

1. Cawello W (ed). Parameters of Compartment-free Pharmacokinetics: Standardisation of Study Design, Data Analysis and Reporting. Shaker Verlag; Aachen, Germany, 1999.
2. Hummel J, McKendrick S, Brindley C, and French R. Exploratory Assessment of Dose Proportionality: Review of Current Approaches and Proposal for a Practical Criterion. Pharmaceut. Statist., Vol. 8, No. 1, January-March 2009. DOI: 10.1002/pst.326.
3. Smith BP, Vandenhende FR, DeSante KA, Farid NA, Welch PA, Callaghan JT, and Forgue ST. Confidence Interval Criteria for Assessment of Dose Proportionality. *Pharm Res* 2000; 17:1278-1283.

8 LIST OF PROPOSED TABLES, AND FIGURES

EXHIBIT 1:
Summary Statistics of Baseline Characteristics

Characteristic	Dose Group 1 (N=)	Dose Group 2 (N=)	All Groups (N=)
Dose (mg)			
Mean (SD)			
Median			
Min, Max			
Gender– n (%)			
Male			
Female			
Age (Years)			
Mean (SD)			
Median			
Min, Max			
Height (cm)			
Mean (SD)			
Median			
Min, Max			
Weight (kg)			
Mean (SD)			
Median			
Min, Max			

EXHIBIT 2:
Individual and Summary Statistics for Oxfendazole (Plasma) Concentrations by Nominal Time (hours)*

	Nominal Time (hrs)													
Subject ID	**Pre-Dose**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**24**	**48**	**72**	**120**	**168**	**336**
001														
002														
003														
N														
Number > LLOQ														
Mean														
SD														
Min														
Median														
Max														

*This table will be repeated for each dose group.
LLOQ = 2 ng/ml
LLOD = 1 ng/ml

EXHIBIT 3:
Individual and Summary Statistics for Fenbendazole (Plasma) Concentrations by Nominal Time (hours)*

Subject ID	Nominal time (hrs)													
	Pre-Dose	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**24**	**48**	**72**	**120**	**168**	**336**
001														
002														
003														
N														
Number > LLOQ														
Mean														
SD														
Min														
Median														
Max														

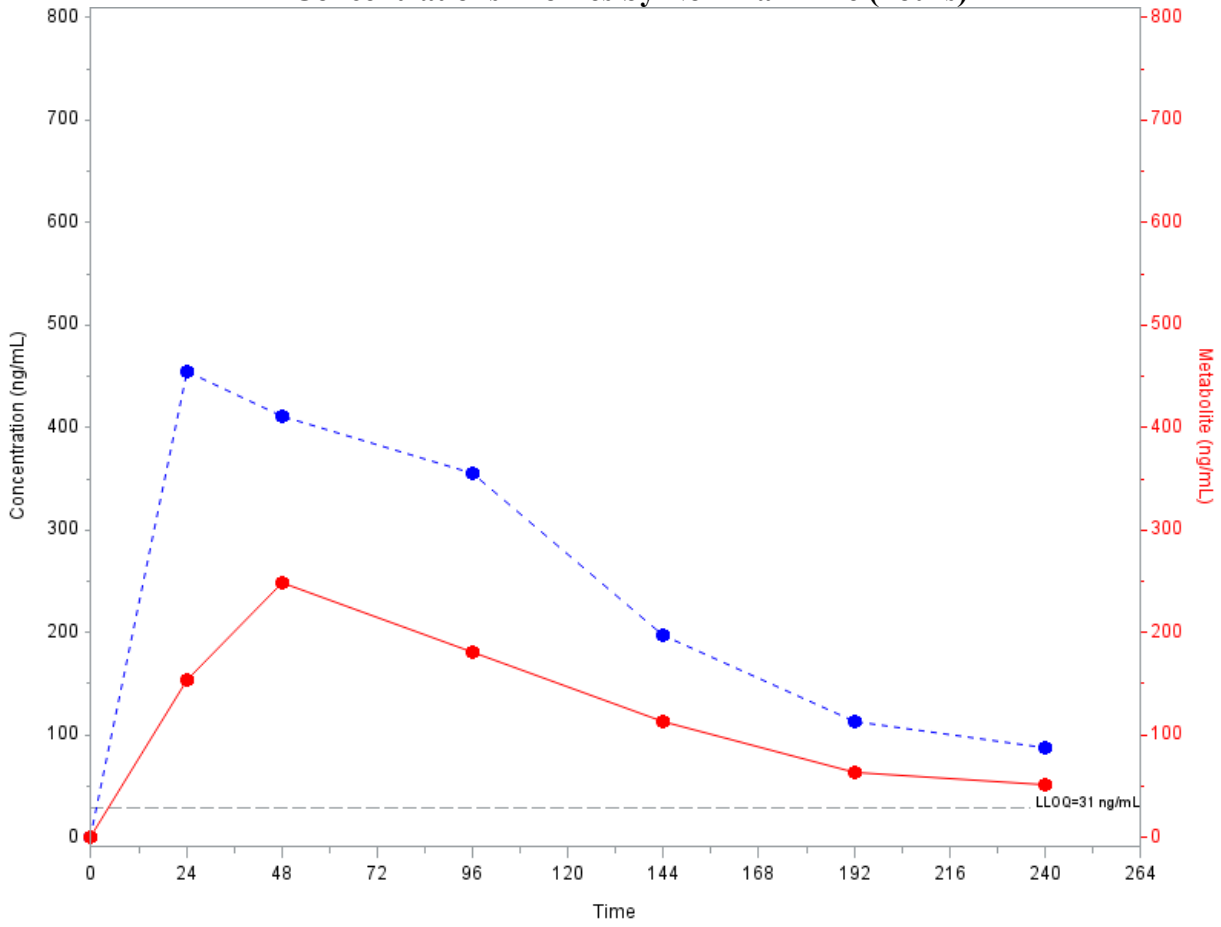
*This table will be repeated for each dose group.
LLOQ = 2 ng/ml
LLOD = 1 ng/ml

EXHIBIT 4:
Individual and Summary Statistics for Sulfone (Plasma) Concentrations by Nominal Time (hours)*

Subject ID	Nominal time (hrs)													
	Pre-Dose	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**24**	**48**	**72**	**120**	**168**	**336**
001														
002														
003														
N														
Number > LLOQ														
Mean														
SD														
Min														
Median														
Max														

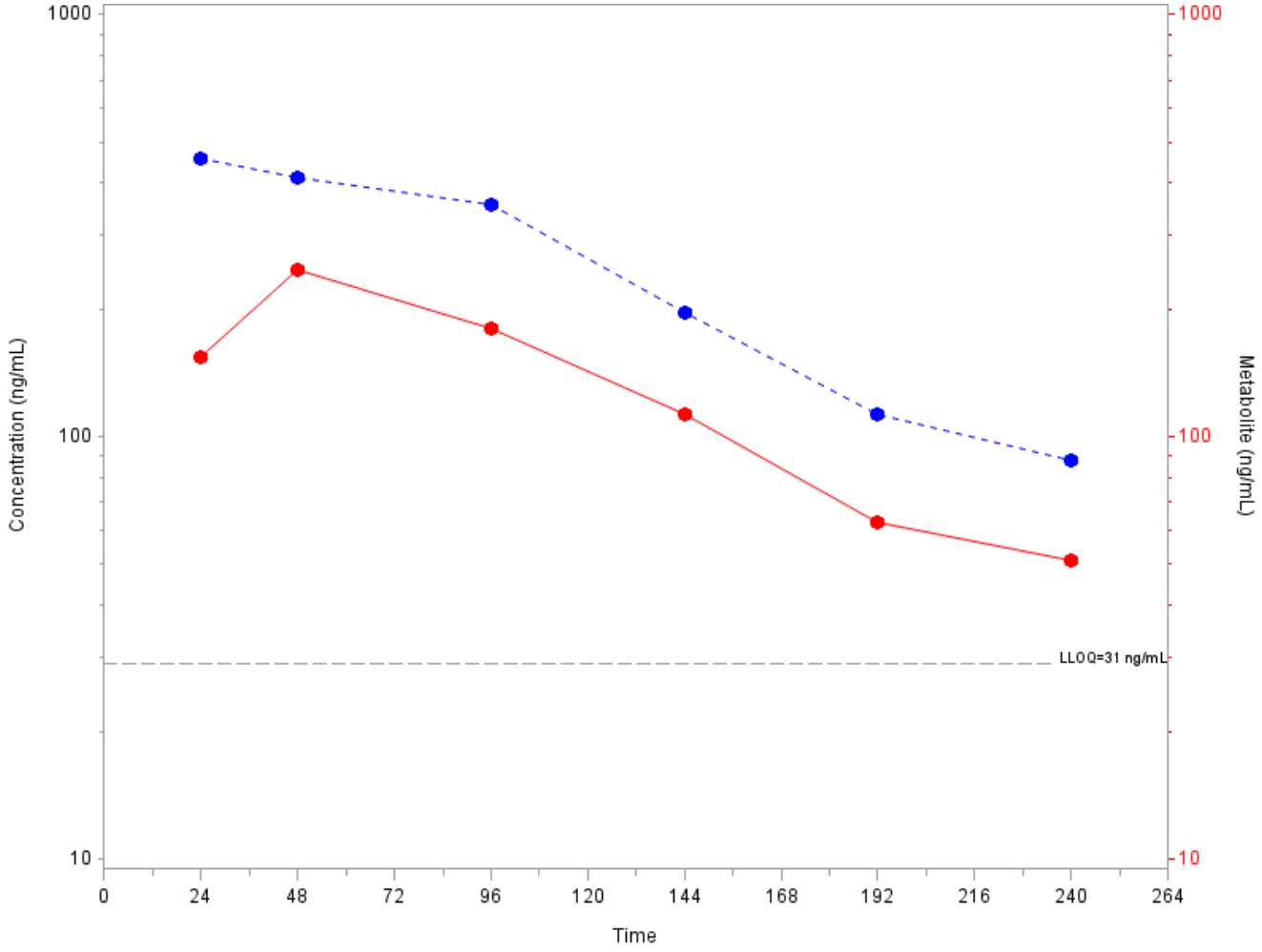
* This table will be repeated for each dose group.
LLOQ = 2 ng/ml
LLOD = 1 ng/ml

EXHIBIT 5:
Concentrations Profiles by Nominal Time (hours)*



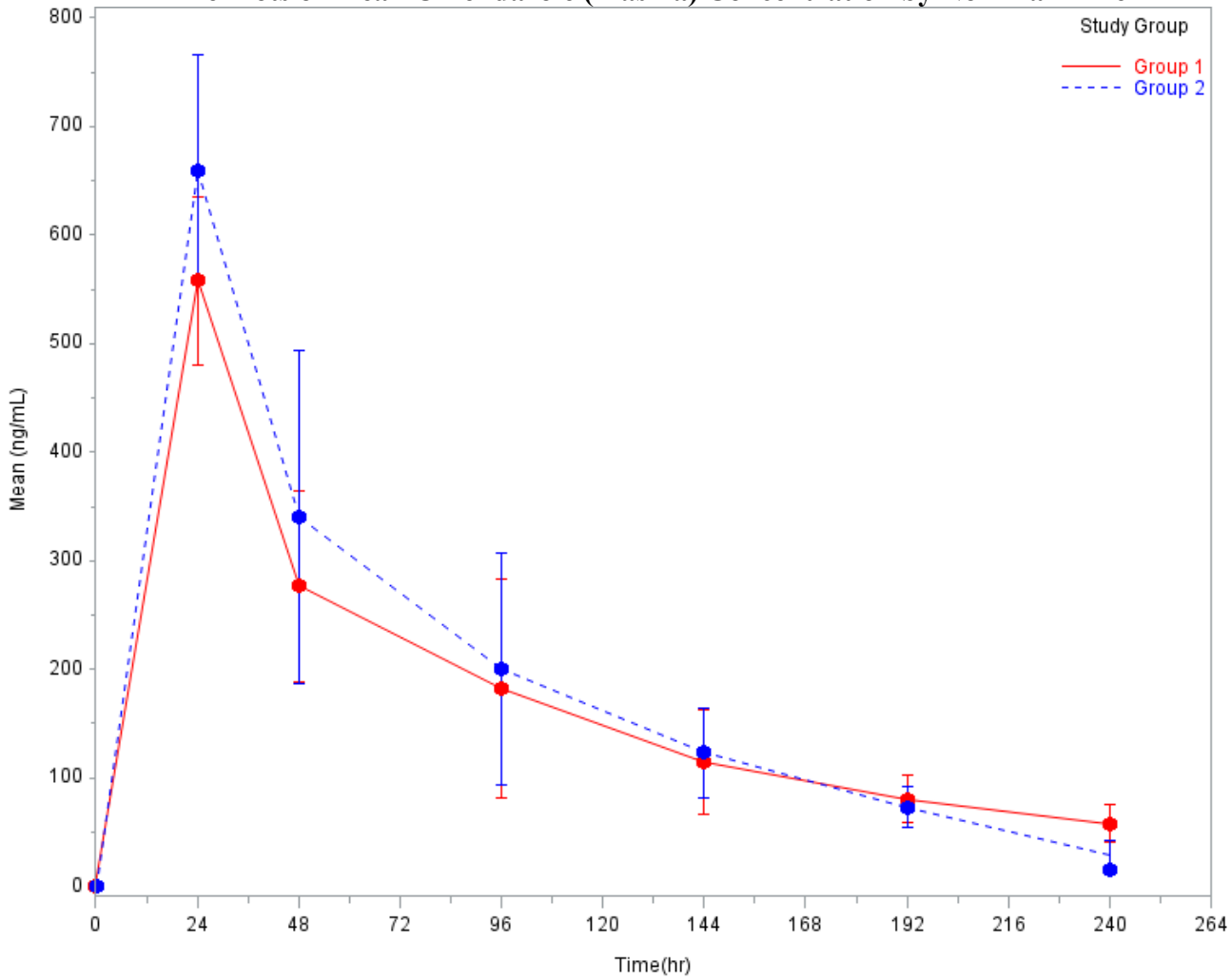
*This figure will be repeated for each subject.

EXHIBIT 6:
Semilogarithmic Individual Concentration Profiles*



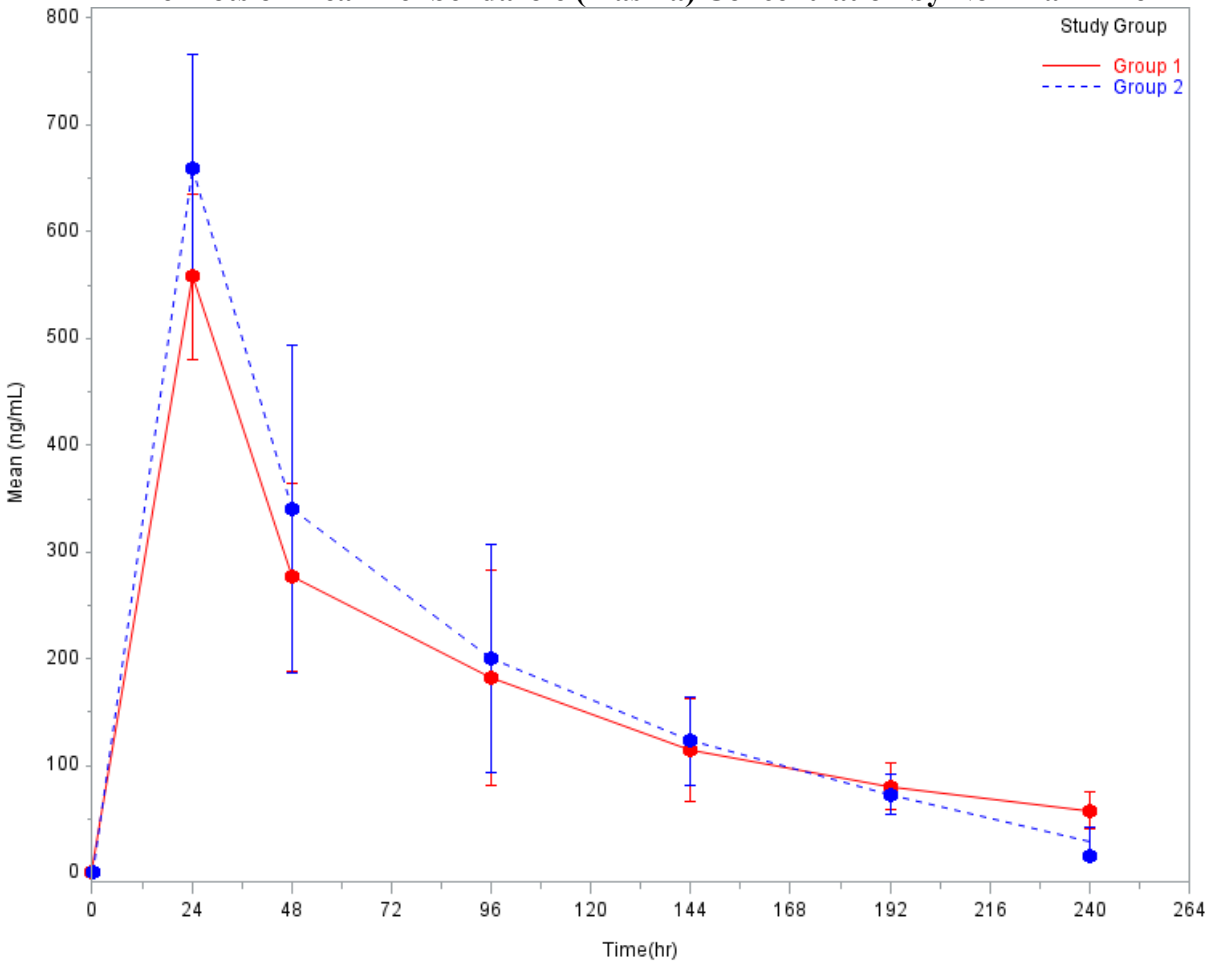
*This figure will be repeated for each subject.

EXHIBIT 7:
Line Plots of Mean Oxfendazole (Plasma) Concentration by Nominal Time*



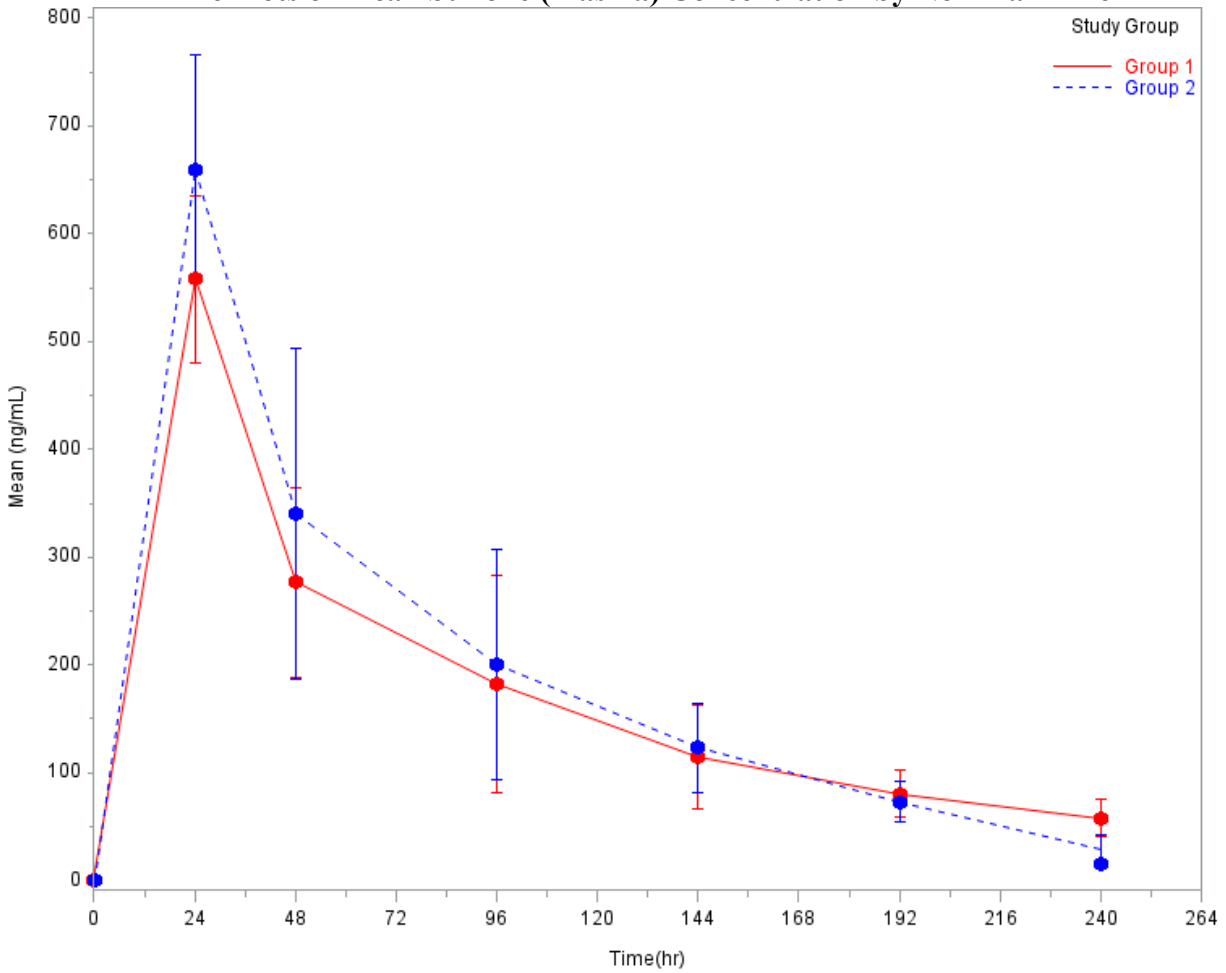
*Error bars give +/- standard deviation.

EXHIBIT 8:
Line Plots of Mean Fenbendazole (Plasma) Concentration by Nominal Time*



*Error bars give +/- standard deviation.

EXHIBIT 9:
Line Plots of Mean Sulfone (Plasma) Concentration by Nominal Time*



*Error bars give +/- standard deviation.

EXHIBIT 10:
Summary Statistics for Cumulative Amount of Oxfendazole Excreted Unchanged in Urine by Nominal Time*

	Pre-Dose	0-4 hours	4-8 hours	8-12 hours	12-24 hours
Statistic					
N					
Mean					
SD					
Min					
Median					
Max					

* This table will be repeated for each dose group.
Subject level data is presented in Listing 2.

EXHIBIT 11:
Summary Statistics for Cumulative Amount of Fenbendazole Excreted Unchanged in Urine by Nominal Time*

	Pre-Dose	0-4 hours	4-8 hours	8-12 hours	12-24 hours
Statistic					
N					
Mean					
SD					
Min					
Median					
Max					

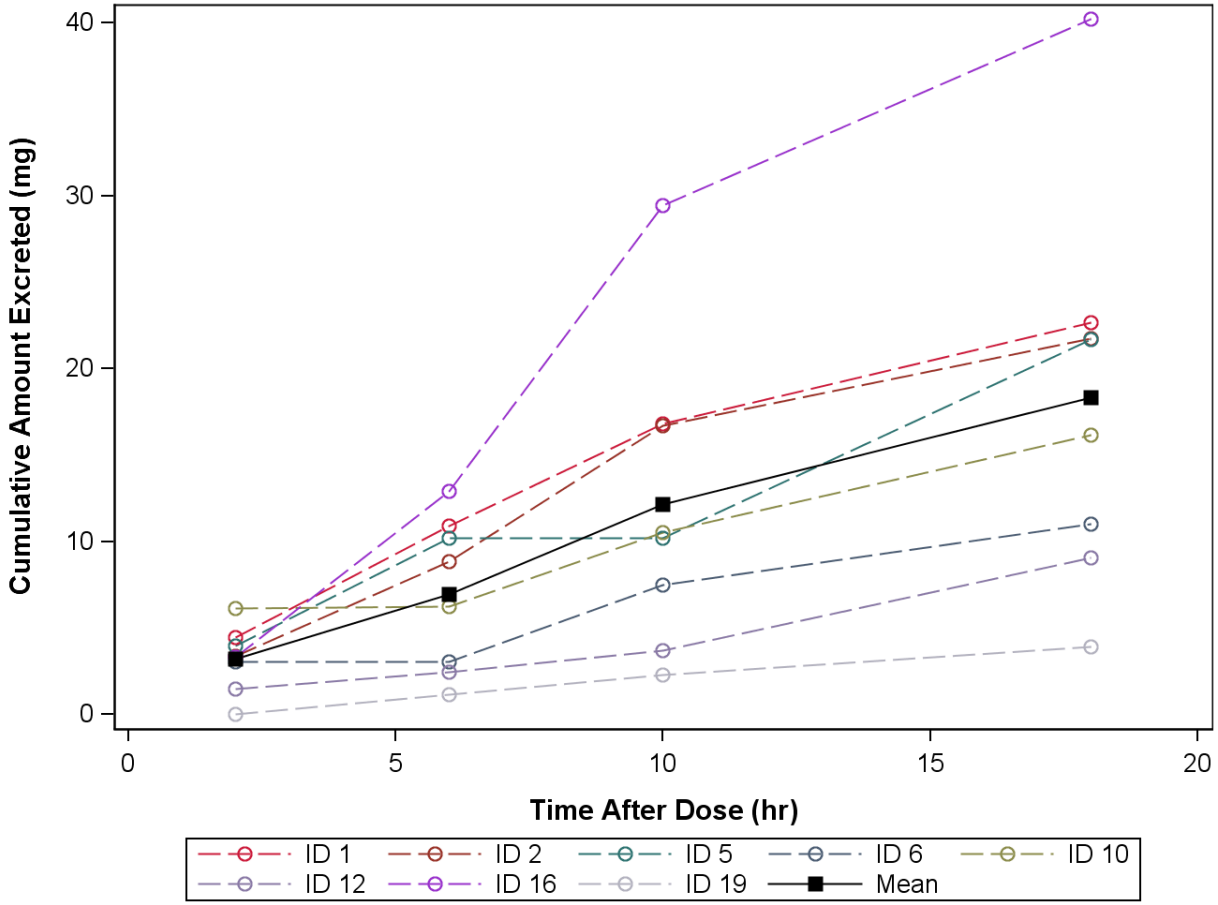
* This table will be repeated for each dose group.
Subject level data is presented in Listing 2.

EXHIBIT 12:
Summary Statistics for Cumulative Amount of Sulfone Excreted Unchanged Urine by Nominal Time*

	Pre-Dose	0-4 hours	4-8 hours	8-12 hours	12-24 hours
Statistic					
N					
Mean					
SD					
Min					
Median					
Max					

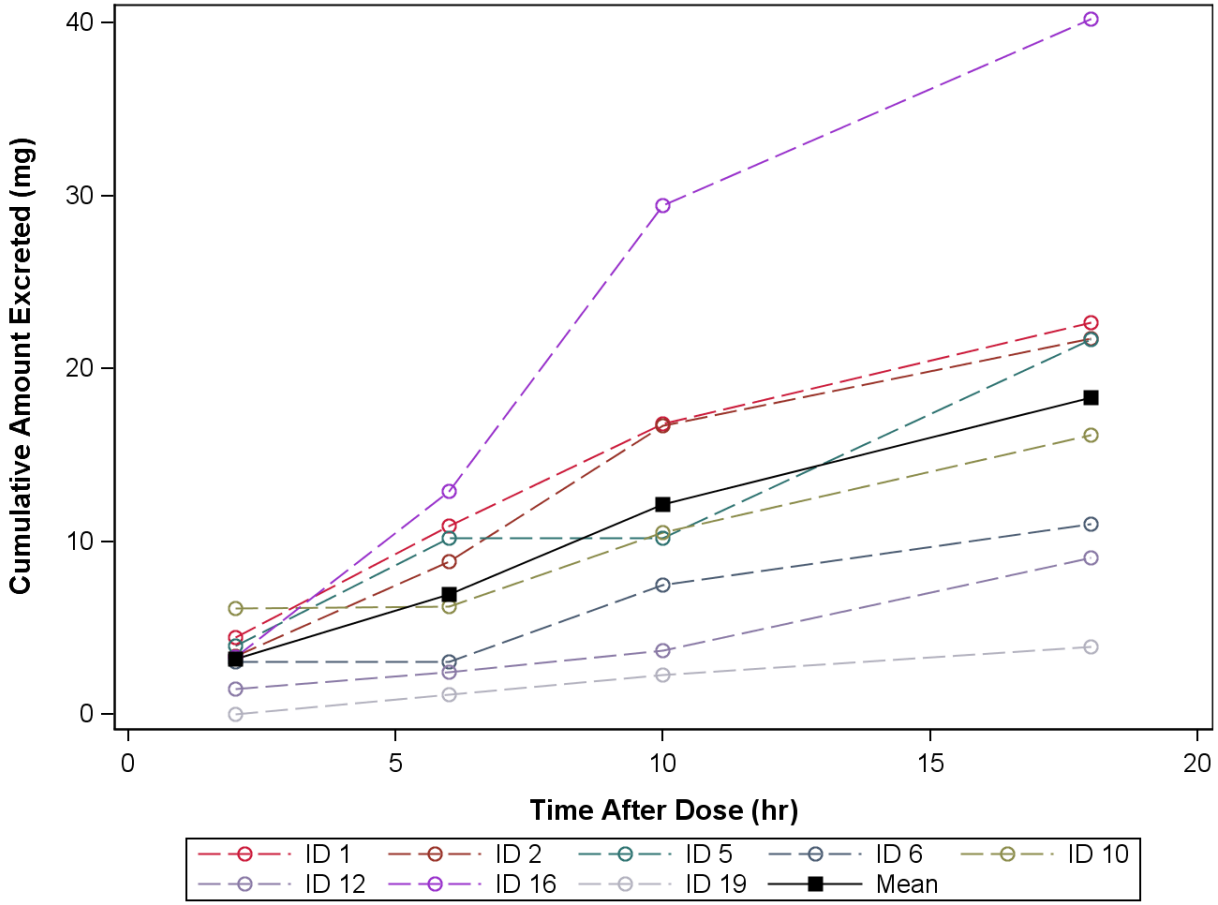
This table will be repeated for each dose group.
Subject level data is presented in Listing 2.

EXHIBIT 13:
Cumulative Amount of Oxfendazole
Excreted Unchanged in Urine by Nominal Time*



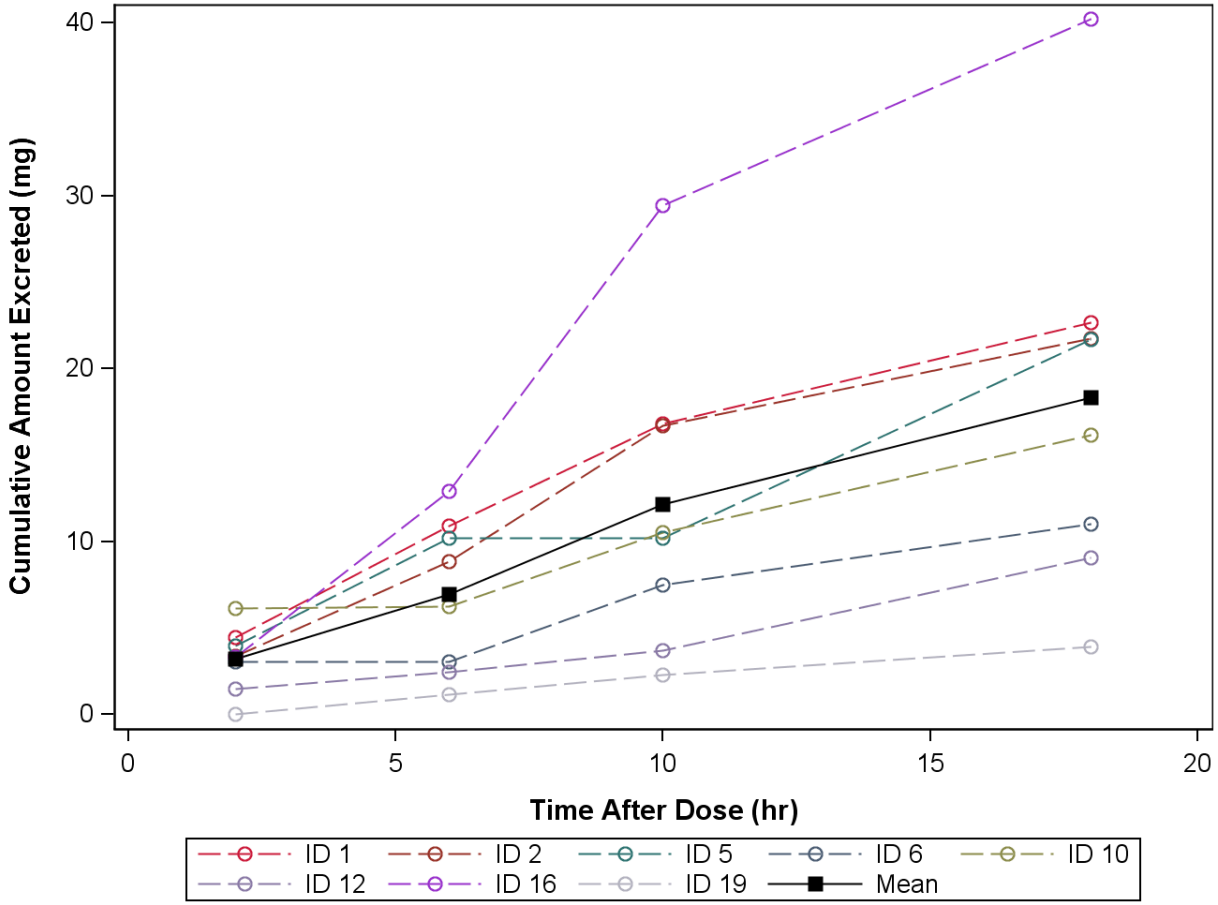
This figure will be repeated for each dose group.

EXHIBIT 14:
Cumulative Amount of Fenbendazole Excreted in Urine by Nominal Time*



This figure will be repeated for each dose group.

EXHIBIT 15:
Summary Statistics for Cumulative Amount of Sulfone Excreted in Urine by Nominal Time*



This figure will be repeated for each dose group.

EXHIBIT 16:
Individual and Summary Statistics for Oxfendazole Noncompartmental PK Parameters*

Subject ID	AUC_{0-t} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	T_{max} (hr)	C_{max} (ng/mL)	N for λ_z	λ_z (hr^{-1})	$t_{1/2}$ (hr)	CL/F (L/hr)	Vz/F (L)	CL_R (L/hr)	fe
001											
002											
003											
N											
Mean											
SD											
Min											
Max											
CV %											
GM											

* This table will be repeated for each dose group.
LLOQ = 2 ng/ml
LLOD = 1 ng/ml
N= number of time points used to calculate λz

EXHIBIT 17:
Individual and Summary Statistics for Fenbendazole Noncompartmental PK Parameters*

Subject ID	AUC_{0-t} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	T_{max} (hr)	C_{max} (ng/mL)	N for λ_z	λ_z (hr^{-1})	$t_{1/2}$ (hr)	CL/F (L/hr)	Vz/F (L)	CL_R (L/hr)	fe
001											
002											
003											
N											
Mean											
SD											
Min											
Max											
CV %											
GM											

* This table will be repeated for each dose group.
LLOQ = 2 ng/ml
LLOD = 1 ng/ml
N= number of time points used to calculate λz

EXHIBIT 18:
Individual and Summary Statistics for Sulfone Noncompartmental PK Parameters*

Subject ID	AUC_{0-t} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	T_{max} (hr)	C_{max} (ng/mL)	N for λ_z	λ_z (hr^{-1})	$t_{1/2}$ (hr)	CL/F (L/hr)	Vz/F (L)	CL_R (L/hr)	fe
001											
002											
003											
N											
Mean											
SD											
Min											
Max											
CV %											
GM											

* This table will be repeated for each dose group.
LLOQ = 2 ng/ml
LLOD = 1 ng/ml
N= number of time points used to calculate λz

LISTING 1:
Subject Level Demographic and Baseline Characteristics

Dose Group	Subject ID	Dose (mg)	Sex	Age (Years)	Weight (kg)	Height (cm)

LISTING 2:
Subject Level Amount Excreted in Urine and Urine Concentrations by Treatment Group and Analyte

									Oxfendazole		Fenbendazole		Sulfone	
Dose Group	Subject ID	Visit Number (Study Day)	Scheduled Collection Interval (hr)	Actual Collection Interval (hr)	Start Date (Time) of Urine Collection	Stop Date (Time) of Urine Collection	Collected Urine Volume (mL)	Date (Time) of Sample Collection	Concentration (ng/mL)	Amount Excreted (mg)	Concentration (ng/mL)	Amount Excreted (mg)	Concentration (ng/mL)	Amount Excreted (mg)