CLINICAL RESEARCH IN INFECTIOUS DISEASES

Clinical Pharmacokinetic Noncompartmental Data Analysis Plan

For

DMID Protocol: 16-0005

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

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

PROTOCOL NUMBER: DMID 16-0005

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ACRONYMS AND ABBREVIATIONS

Standard acronyms and abbreviations are listed below.

Abbreviation	Definition
AIC	Akaike Information Criterion
AUC	Area Under the Concentration-Time Curve
AUC_{last}	AUC to the Last Measurable Concentration
$AUC_{0-\infty}$	AUC Extrapolated to Infinity
AUC_{τ}	AUC of Dosing Interval
BA	Bioavailability
BE	Bioequivalence
BMI	Body Mass Index
BQL	Below the Quantification Limit
C_{last}	Last measurable concentration (above the quantification limit)
CL	Clearance
CL/F	Apparent Oral Clearance
C_{max}	Maximum Concentration
C_{trough}	Pre-dose Trough Concentration
CSR	Clinical Study Report
CV	Coefficient of Variation
F	Bioavailability
FDA	Food and Drug Administration
GM	Geometric Mean
hr	Hour
λ_z	Terminal Phase Elimination Rate Constant
LC/MS/MS	Liquid Chromatography-tandem Mass Spectrometry
LOD	Limit of Detection
LLOQ	Lower Limit of Quantification
Max	Maximum
Min	Minimum
NCA	Noncompartmental Analysis
PD	Pharmacodynamic
PK	Pharmacokinetic
AR	Accumulation Ratio
SD	Standard Deviation
SS	Steady State
τ	Length of the Dosing Interval
$t_{1/2}$	Apparent Terminal Elimination Half-Life
T_{last}	Time of Last Measurable Concentration
T_{max}	Time to Obtain Maximum Concentration (C_{max})
V_d/F	Apparent Volume of Distribution

1. PREFACE

DMID Protocol 16-0005 is a Phase I study of oxfendazole in healthy adult volunteers. The pharmacokinetic (PK)-related objectives of the study are:

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

This document reiterates key PK elements in the study design of 16-0005 and thoroughly describes the presentations and summaries of PK data as well as the noncompartmental analysis (NCA) to be included in a PK Report or in the clinical study report (CSR). Shells and mockups are given for all tables, figures, and listings planned for inclusion in the report.

Any deviation from this statistical plan will be described and justified in protocol amendments and/or in the 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.

2. CLINICAL STUDY METHODS

2.1. Treatment Groups

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 crossover 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 trial, each dose group will be comprised of 8 subjects, all of whom will receive study product once daily for 5 days. To enhance safety, 1 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 6 subjects in this group will be enrolled. All volunteers will be followed for 10 days and PK, safety laboratory and EKG studies will be performed. If no predefined safety events occur after all 8 subjects have completed the Day 10 visit, the DMID Medical Monitor will issue approval to proceed with enrollment of the second group of 8 subjects, who will receive 5 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 8 subjects will be enrolled to receive 5 days of 15 mg/kg using the same enrollment plan.

In the second phase of the study evaluating the effects of food on drug absorption, 12 subjects will be enrolled into a randomized, single dose, two-period, two-treatment (2x2) crossover trial. In the first period of this trial, 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 breakfast. After a one-week wash-out period, subjects will cross over in the second period to receive a single dose following a high fat breakfast or 8 hour fast. The order of conditions, Sequence A (fasted condition first) and Sequence B (fed condition first), will be randomly assigned upon enrollment in a 1:1 ratio.

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, a replacement subject will be enrolled and randomized.

2.2. Dose Administration

In the first phase of the study, subjects will be administered oxfendazole q24 hours via oral syringe by a study nurse or investigator on Days 1, 2, 3, 4 and 5. Subjects will be fasting (water is permitted) for 8 hours prior to, and for 2 hours after, the administration of drug

In the second phase, 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. After 7 days, each subject will cross over to receive a single dose of oxfendazole (3mg/kg) following either a high fat meal or following an 8 hour fast. Subjects receiving a high fat meal will be administered study product approximately 30 minutes (+/- 15 minutes) following completion of the meal. Subjects who fasted prior to receiving study product will remain fasting for 2 hours after 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.

Subjects in both phases of the study will be provided lunch and dinner on day of dosing. If vomiting occurs following ingestion of the study product, that dose will not be replaced. All subjects will be counseled to avoid drug, alcohol, and tobacco use through the end of the study.

Additional details regarding study product administration can be found in the protocol and Manual of Procedures (MOP).

2.3. PK Sampling Schedule Treatment Groups

For the first phase of the study (Groups 1-3), 10 mL of blood for oxfendazole level will be drawn pre-dose and at 30 minutes, 1, 2, 3, 4, 6, 9, and 12 hours following the first dose. All times have a window of +/- 15 minutes except the 9 and 12 hour samples which have a window of +/- 30 minutes. On Days 2, 3, and 4, blood will be sampled for oxfendazole level approximately 24 hours (+/- 4 hours for Day 2, +/- 2 hours for Days 3 and 4) after the prior dose, but before the current study day dose. On Days 2, 3, and 4, approximately 2 hours (+/- 20 minutes) after administration of study drug, blood will be drawn for oxfendazole level. On Day 5, blood will be sampled pre-dose (24 hours +/- 2 hours after the prior dose) 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). Blood will also be sampled for oxfendazole level on Day 6, approximately 24 hours after dosing on Day 5 (+/- 6 hours) and Days 8 (+/- 1 day) and 10 (+/- 2 days).

In the second phase of the study (Group 4), blood sampling for oxfendazole level will be performed pre-dose and at 30 minutes, 1, 2, 3, 4, 5, 9, 12 and 24 hours following each dose on Day 1 and Day 8 (+/- 1 day). All times have a window of +/- 15 minutes except the 9 and 12

hour samples which have a window of +/- 30 minutes and the 24-hour sample which has a window of +/- 4 hours. Blood will also be sampled for oxfendazole level on Day 14 (+/- 2 days).

The exact time for all blood draws for oxfendazole level will be recorded and used for pharmacokinetic noncompartmental analysis (NCA).

2.4. Analytical Methods

Measurement of oxfendazole plasma concentrations will be performed by the Dr. Guohua An's Pharmacokinetics & Pharmacodynamics laboratory at the University of Iowa using a validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) method for quantification of oxfendazole in human plasma with sodium heparin with lower limit of quantification (LLOQ) of 0.5 ng/mL.

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 minutes. The plasma will then be collected and stored frozen at –80°C until analyzed. Plasma samples will be shipped to the analytical lab frozen.

2.5. Collection of Pharmacodynamic or Clinical Endpoints

Not applicable.

3. PHARMACOKINETIC ANALYSIS METHODS

3.1. Analysis Populations and Handling of Missing Time Points

All subjects receiving study drug and having at least 1 measurable drug concentration will be included in the multiple ascending dose study PK population or the food effect study PK population, as appropriate. If there are subjects who do not have sufficient samples for a complete analysis, a modified analysis will be conducted in which some or all PK parameters may not be estimated for those subjects, but available PK concentrations will still be tabulated and graphed.

If any subjects are found to be noncompliant with respect to dosing, have incomplete data, or experience an event that is likely to affect PK, the Sponsor, the Investigator, and the Statistician will determine their inclusion into the population on a case-by-case basis. Subjects excluded from the PK analyses and their reasons for exclusion will be denoted and detailed.

PK sample concentrations identified as laboratory errors will be indicated as such in the report and may be excluded from analyses. Time points below the lower limit of quantification (LLOQ) preceding the first PK concentration above the LLOQ will be imputed as 0. Pharmacokinetically plausible concentration value(s) below LLOQ at time points between two measurable concentration values (e.g., at trough timepoints) will be replaced by the LLOQ/2 value for graphing purposes only, and treated as missing for analyses. All other PK sample concentrations below the LLOQ will be treated as missing for analyses. Missing PK sample concentrations will not be imputed for the NCA. A geometric mean of concentrations will be treated as missing for sets of data points containing a below the quantification limit (BQL) value.

3.2. Demographic and Baseline Characteristics

Sex, race, age, weight, height, and body mass index (BMI) of subjects in the PK population will be listed and summarized by treatment group (Listing 1, Table 1, and Table 2).

3.3. Dosing and Pharmacokinetic Sampling Summary

Subject dose administration times will be presented (Listing 2). Special cases that potentially affect the analysis will be discussed. Drug plasma concentrations will be listed by group and subject, with BQL, out of sample time window, and PK analyses-excluded samples indicated (Listing 3). The listings will also indicate, for each sample, the associated dose number, nominal and actual time since first dose, and actual time since the preceding dose.

Important protocol deviations related to dosing or PK sampling will be discussed. Potentially important bioanalytical errors and their effect on the PK analysis will also be discussed.

For Groups 1-3, Table 3, Table 4, and Table 5 will list and summarize drug concentrations for Dose 1 and Table 6, Table 7, and Table 8 will summarize drug concentrations for Dose 5. As only peak and trough concentrations are measured for doses 2-4, these concentrations will be

displayed in Table 9, Table 10, and Table 11. For Group 4, Table 12, Table 13, Table 14, and Table 15 will list and summarize drug concentrations by sequence and period.

The following figures will display concentration data for the multiple ascending dose phase (Groups 1-3):

- Linear scale concentration profiles of all subjects, color-coded by dose group (Figure 1)
- Linear plot of mean concentration for each dose group over time, with error bars representing standard deviation, color-coded by dose group (Figure 3)
- Linear scale concentration profile for each subject individually, repeated for all subjects (Figure 5)
- Data from Figures 1, 3 and 5 will be presented on a semi-log scale in Figure 2, Figure 4, and Figure 6.

The following figures will display concentration data for the second phase evaluating food effects (Group 4):

- Linear scale concentration profiles of all subjects, displayed by sequence and period (Figure 7)
- Linear plot of mean concentration for each condition over time, with error bars representing standard deviation, color-coded by condition (Figure 9)
- Linear scale concentration profile of each condition for each subject individually, repeated for all subjects (Figure 11)
- Data from Figure 7, Figure 9, and Figure 11 will be presented on a semi-log scale in Figure 8, Figure 10 and Figure 12.

3.4. Definition and Estimation of Individual PK Parameters

The PK parameters listed below will be estimated through a NCA using version 8.0 of Phoenix WinNonlin (Pharsight Corporation, Cary, NC). Actual post-dose time will be used for the estimation of PK parameters instead of nominal time. Subject-specific PK parameters will be presented (Table 16, Table 17, Table 18, Table 19, Table 20, Table 21, Table 22 Table 27 , Listing 3, Listing 4, and Listing 5).

Phoenix WinNonlin NCA will use the following settings to compute parameters from plasma PK data:

- Linear Up Log Down calculation method
- Uniform weighting
- Extravascular dose
- Lambda Z Acceptance Criteria
  - Rsq_adjusted ≥ 0.85
  - Span ≥ 1.5 half-lives

C_{max}

Maximum concentration (C_{max}) is defined as the maximum observed drug concentration observed over all PK sample concentrations for a given dose, and will be obtained from the **Cmax** parameter calculated by Phoenix WinNonlin.

C_{trough}

Pre-dose trough concentration (C_{trough}) is defined as the drug concentration observed at the last planned timepoint prior to dosing. Since there is no dose following Day 5, C_{trough} for that day is defined as the concentration 24 hours (nominal time) after dosing.

T_{max}

Time of maximum concentration (T_{max}) is defined as the time at which the maximum concentration occurs within the given dosing interval and will be obtained from the **Tmax** parameter calculated by Phoenix WinNonlin.

λ_z

The terminal phase elimination rate constant (λ_z) is defined as the first-order rate constant describing the rate of decrease of drug concentration in the terminal phase (defined as the terminal region of the PK curve where drug concentration follows first-order elimination kinetics), and will be obtained from the **Lambda_z** parameter calculated by Phoenix WinNonlin.

λ_z will be computed as the slope of a terminal region consisting of at least 3 successive points in the plot of log-transformed concentration data versus time. λ_z will be estimated using uniform weighting. Time points used in the estimation of λ_z will be initially selected using the Phoenix WinNonlin automatic algorithm. The set of points chosen must contain only timepoints after T_{max}, include at least 3 timepoints, and satisfy the Lambda Z Acceptance Criteria described above. The range of concentrations used to estimate λ_z for each profile will be inspected by the PK analyst, and the PK analyst may adjust the set of concentrations used to estimate λ_z if deemed necessary, but manually selected ranges must satisfy the same acceptance criteria as those chosen automatically by the Phoenix WinNonlin algorithm.

Drug concentrations used to calculate λ_z will be indicated in Listing 3.

λ_z will be estimated for Doses 1 and 5 in Groups 1, 2, and 3, and for Group 4.

$t_{½}$

The apparent terminal elimination half-life ($t_{½}$) is defined as the time required for the drug concentration to decrease by a factor of one-half in the terminal phase. The apparent terminal elimination half-life ($t_{½}$) will be estimated as ln (2) / λ_z and will be obtained from the **HL_Lambda_z** parameter calculated by Phoenix WinNonlin. $t_{½}$ will be estimated for Doses 1 and 5 in Groups 1, 2, and 3, and for Group 4, when λ_z is estimable.

AUC

AUC is defined as the area under the concentration-time curve. AUC will be estimated using the Linear Up Log Down calculation method.

AUC_{τ}

AUC_{τ} is defined as AUC of a single dosing period. In groups 1-3, AUC_{τ} for a given dose will be calculated as AUC from time of dosing to the end of the 24-hour dosing interval for Dose 1 and Dose 5. AUC_{τ} will be obtained in Phoenix WinNonlin using the Partial Area functionality.

AUC_{last}

AUC_{last} is defined as the AUC from dosing to the time of the last measured concentration ≥ LLOQ (C_{last}) of that dosing period and will be obtained from the **AUClast** parameter calculated by Phoenix WinNonlin.

$AUC_{(0-\infty)}$

$AUC_{(0-\infty)}$ is defined as the AUC from dosing taken to the limit as the end time becomes arbitrarily large. $AUC_{(0-\infty)}$ for a given dose will be estimated by adding AUC_{last} for that dose to an extrapolated value equal to the last measured concentration greater than the LLOQ divided by λ_z:

$$AUC_{(0-\infty)} = AUC_{last} + \frac{C_{last}}{\lambda_Z},$$

where C_{last} is the last measured concentration ≥ LLOQ. $AUC_{(0-\infty)}$ will be obtained from the **AUCINF_obs** parameter calculated by Phoenix WinNonlin If the amount extrapolated portion of $AUC_{(0-\infty)}$ is >25%, the estimated $AUC_{(0-\infty)}$ value will be flagged when listed in the report and will be excluded from downstream statistical analyses, but included in the calculation of summary statistics.

AUC_{τ}, will be estimated for Dose 1 and Dose 5 in Groups 1, 2, and 3. AUC_{last} will be estimated for Dose 5 in Groups 1, 2 and 3, and for Group 4. $AUC_{(0-\infty)}$ will be estimated for Group 4 when λ_z is estimable.

CL/F

For Group 4, apparent oral clearance (CL/F) will be calculated as Dose/$AUC_{(0-\infty)}$ and will be obtained from the **CL_F** parameter in Phoenix WinNonlin. If the amount extrapolated portion of $AUC_{(0-\infty)}$ is >25%, the estimated CL/F value will be flagged when listed in the report, but included in the calculation of summary statistics.

CL_{SS}/F

For Groups 1, 2 and 3, apparent oral clearance at steady state (CL_{SS}/F) will be calculated as the dose in mg/kg divided by the AUC_{τ} for Dose 5 (expected steady state) and will be obtained from the **Clss_F** parameter calculated by Phoenix WinNonlin.

$$CL_{SS}/F = \frac{Dose}{AUC_{\tau,\ Dose\ 5}}$$

V_d/F

For Group 4, apparent volume of distribution (V_d/F) will be calculated as (CL/F)/ λ_z and will be obtained from the **Vz_F** parameter in Phoenix WinNonlin. If the amount extrapolated portion of $AUC_{(0-\infty)}$ is >25%, the estimated V_d/F value will be flagged when listed in the report, but included in the calculation of summary statistics.

AR

For Groups 1, 2 and 3, the observed accumulation ratio (AR) is defined as the ratio of exposure parameters following multiple and single dosing. AR will be calculated using AUC_τ and C_{max}:

$$AR = \frac{AUC_{\tau,\ Dose\ 5}}{AUC_{\tau,\ Dose\ 1}},$$

$$AR = \frac{C_{max,\ Dose\ 5}}{C_{max,\ Dose\ 1}}$$

When λ_Z is estimable, AR will also be estimated using the elimination rate λz from Dose 5:

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

where τ is the length of the dosing interval, 24 hours.

3.5. Descriptive Statistics and Inference of PK Parameters

3.5.1. Pharmacokinetic Parameter Summaries

All PK parameters will be summarized using descriptive statistics: N, Mean, standard deviation (SD), Min, Max, Median, coefficient of variation as a percent (CV %), and geometric mean (GM). A subset of PK parameters will be summarized by dose and dose group where appropriate (Table 16, Table 17, Table 18, Table 19, Table 20, and Table 21). Group 4 parameters will be summarized by condition (Table 22).

3.5.2. Analysis of Sex Differences in PK

This study was not designed to formally assess differences in PK by sex. During the course of this study, preclinical evidence suggestive of sex-based differences in PK became available (communication with Sponsor). To facilitate a descriptive comparison of PK by sex, select PK parameters will be summarized by dose, dose group, and sex (Table 24 and Table 25). Group 4 parameters will be summarized by condition and sex (Table 25). AUC_τ, C_{max} and C_{trough} will also be presented graphically by dose, dose group, and sex in box plots for Groups 1, 2 and 3 (Figure 13, Figure 14, and Figure 15). Box plots of AUC_{last} and C_{max} will be presented by sex and fed/fasted condition for Group 4 (Figure 16). Scatter plots of AUC_τ, C_{max} and C_{trough} by dose, dose group, weight, and sex will also be presented for Groups 1, 2, and 3 (Figure 17, Figure 18 ,

and Figure 19). Scatter plots of AUC_{last} and C_{max} will be presented by weight, sex, and fed/fasted condition for Group 4 (Figure 20).

For the statistical models described in Sections 3.5.3 and 3.5.5, sex will be added as a covariate. The models with and without the additional covariate for sex will be compared, and the final model will be chosen based on Akaike Information Criterion (AIC) and graphical diagnostics of model assumptions and fit.

3.5.3. Attainment of Steady State

Attainment of steady state by Dose 5 will be assessed by visual examination of the concentration versus time plots (Figure 1, Figure 2, Figure 3, Figure 4, Figure 5, and Figure 6).

Graphical findings will be supported by statistical comparison of C_{max} and C_{trough} values on Day 5 with the corresponding values on Day 4 and Day 3. C_{max} and C_{trough} will be log-transformed and analyzed using the following mixed effects model for Y_{ijk}, the log-transformed exposure parameter observed on the kth subject on day j of dose group i:

$$Y_{ijk} = \mu + \pi_j + \lambda_i + \tau_{d[i,j]} + s_{ik} + \varepsilon_{ijk}$$

where μ is the intercept; π_j is a fixed effect associated with day j; λ_i is a fixed effect associated with dose group i, $\tau_{d[i,j]}$ is a fixed effect associated with the interaction of day j and dose group i; s_{ik} is a random effect associated with the kth subject in dose group i, and e_{ijk} is a random error term with mean 0 and variance σ_e^2. This model will be fit using restricted maximum likelihood estimation (REML) in SAS PROC MIXED, with the Kenward and Roger denominator degrees of freedom.[1] Covariance structure will be selected based on AIC, from the following candidate structures: variance components, first-order autoregressive, compound symmetry, Toeplitz, and unstructured. SAS code will be similar to:

```
PROC MIXED;
    CLASS DAY DOSEGROUP SUBJECT;
    MODEL LCMAX = DAY DOSEGROUP DAY*DOSEGROUP / DDFM=KR;
    RANDOM SUBJECT / TYPE = VC;
    LSMEANS DAY*DOSEGROUP / PDIFF CL;
RUN;
```

The mean difference in log-transformed parameter (C_{max} or C_{trough}) between Day 5 and each of Days 4 and 3 at each dose level will be back transformed to obtain the geometric mean ratio. Contrasts of model parameters will be used to generate 95% confidence intervals for the geometric mean ratios. The geometric mean ratios and corresponding confidence intervals will be graphically depicted in Figure 25 and reported in Table 26, alongside the p-value for the hypothesis test of no difference in log-transformed C_{max} and C_{trough} between Day 5 and each of Days 4 and 3 at each dose level.

3.5.4. Summary of Accumulation upon Multiple Dosing

Accumulation ratio will be summarized for each dose group in Groups 1-3 (Table 27).

3.5.5. Analysis of Dose Proportionality

The presence of dose proportionality over the range of studied dose levels for Groups 1-3 will be assessed using the exposure parameters AUC_τ, C_{max}, and C_{trough} of Dose 1 and at expected steady-state (Dose 5). Analysis will be conducted with the power model as described by Smith et al[2]:

$$AUC_\tau = e^\alpha \times dose^\beta.$$

Let ρ be the ratio (highest dose studied / lowest dose studied) and let (L, U) represent the 90% confidence interval for $\hat{\beta}$. In the presence of dose proportionality, $\rho^{\hat{\beta}-1} = 1$. Accordingly, using the bioequivalence criteria of the current FDA guidance[3], dose proportionality across the studied dose range is concluded when:

$$\Theta_l = 0.8 \le \rho^{L-1} < \rho^{U-1} \le 1.25 = \Theta_h.$$

Or, equivalently,

$$1 + \frac{\ln 0.8}{\ln \rho} \le L < U \le 1 + \frac{\ln 1.25}{\ln \rho}.$$

Dose proportionality using C_{max} and C_{trough} will also be assessed using the same approach. Point estimates and 90% confidence intervals for $\hat{\beta}$ will be presented (Table 28). Predicted values from the power model including 90% prediction bands will be overlaid on plots of exposure data (AUC_τ, C_{max}) by dose in mg/kg (Figure 21, Figure 22). Additionally, ANOVA on the log-transformed parameters will be used to construct confidence intervals of the geometric means of dose-adjusted AUC_τ and C_{max} by dose, which will be displayed in Table 29 and plotted side-by-side in order of increasing dosage (Figure 23, Figure 24).

3.5.6. Analysis of Changes in T_{max} by Dose Number and Dose Level

Shift in T_{max} between Dose 1 and Dose 5 for Groups 1, 2 and 3 will be tested using the Wilcoxon signed-rank test procedure. Point estimates of the shift (the Hodges-Lehmann estimator) and associated 90% confidence intervals will be provided (Table 30). A test for any difference in T_{max} among the three studied dose levels will be performed using the Kruskal-Wallis one-way ANOVA on ranks.

3.5.7. Analysis of Food Effect

Determination of the effect of food on the kinetics of oxfendazole in Group 4 will be conducted in accordance with current FDA guidance[3,4]. Key exposure parameters ($AUC_{(0-\infty)}$, $AUC_{(0-last)}$, and C_{max}) will be log-transformed and analyzed using the following mixed effects model for Y_{ijk}, the log-transformed exposure parameter observed for the *i*th condition (fed/fasted) for the *k*th subject in period *j*:

$$Y_{ijk} = \mu + \pi_j + \lambda_{d[i,j]} + \tau_{d[i,j]} + s_k + \varepsilon_{ijk}$$

where μ is an intercept; π_j is a fixed effect associated with period j; λ_i is a fixed effect associated with the condition i, $\tau_{d[i,j]}$ is a fixed effect associated with the interaction of period j and condition i; and s_{ik} is a random effect associated with the kth subject with mean 0 and variance σ_s^2, and e_{ijk} is a random error term with mean 0 and variance σ_e^2.

The model will be fit using REML in SAS PROC MIXED. Point estimates and 90% confidence intervals for the mean difference between fed and fasted conditions will be constructed for each log-transformed exposure parameter. SAS code will be similar to:

```
PROC MIXED;
    CLASS PERIOD CONDITION SUBJECT;
    MODEL LCMAX = PERIOD CONDITION PERIOD*CONDITION / DDFM=KR;
    RANDOM SUBJECT;
    LSMEANS CONDITION / ALPHA=0.1 PDIFF CL;
RUN;
```

Point and interval estimates of the mean difference in log-transformed exposure parameters will then be back-transformed to obtain point estimates and 90% confidence intervals for the ratio of geometric means of the parameters. Equivalence between the fasting and fed conditions will be based on whether the 90% confidence interval for the ratio of the population geometric mean of the parameter measured from the 2 conditions is contained in the interval [0.80, 1.25].

In addition, for each exposure parameter, the intrasubject coefficient of variation (CV_W) will be calculated to provide an estimate of the variability in exposure within the same subject, when the subject is administered one dose of study product on two separate occasions.

For normally distributed data with mean μ and variance σ^2, coefficient of variation is defined as:

$$CV = \sqrt{Var\left(\frac{X - \mu}{\mu}\right)} = \frac{\sigma}{\mu} = \frac{\sqrt{Var(X)}}{E(X)}$$

If X is instead distributed log-normally (i.e., Y = log(X) is normally distributed with mean μ and variance σ^2), then:

$$E(X) = \exp\left(\mu + \frac{\sigma^2}{2}\right)$$

$$Var(X) = [\exp(\sigma^2) - 1]\exp(2\mu + \sigma^2)$$

The coefficient of variation can be written in terms of σ^2 as:

$$CV = \frac{\sqrt{Var(X)}}{E(X)} = \frac{\left[\sqrt{\exp(\sigma^2) - 1}\right]\exp\left(\mu + \frac{\sigma^2}{2}\right)}{\exp\left(\mu + \frac{\sigma^2}{2}\right)} = \sqrt{\exp(\sigma^2) - 1}$$

Thus, the intrasubject coefficient of variation can be estimated from the model on log-transformed data as:

$$\widehat{CV_W} = \sqrt{\exp(MSE) - 1}$$

where MSE is the residual mean squared error from the model. Results from the statistical analysis of food effect will be shown in Table 31.

Distributional assumptions and homoscedasticity will be assessed by residual plots and/or other graphical diagnostics. Alternative analyses will be considered if assumptions are violated.

Food effect on T_{max} will be assessed with the Wilcoxon signed-rank test procedure. The Hodges-Lehmann estimator (pseudomedian) for the difference in T_{max} between fed and fasted conditions will be reported, as well as the associated 90% confidence interval will be displayed in Table 32. Potential differences in T_{max} due to sequence effects will be explored graphically.

3.6. Comparison of Current Pharmacokinetic Results to Pharmacokinetic Results from Previous Studies

Not applicable.

4. REFERENCES

1. Kenward, M. G. and Roger, J. H. Small sample inference for fixed effects estimators from restricted maximum likelihood. Biometrics 53 (1997): 983-997.
2. Smith, Brian P., et al. Confidence interval criteria for assessment of dose proportionality. Pharmaceutical Research 17.10 (2000): 1278-1283.
3. Food and Drug Administration. Guidance for Industry: Statistical Approaches to Establishing Bioequivalence, January 2001.
4. Food and Drug Administration. Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies, December 2002.
5. Food and Drug Administration. Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations, March 2003.

5. LISTING OF PROPOSED TABLES, FIGURES, AND LISTINGS

Proposed table, figure, and listing shells are presented in Appendices I, II, and III.

6. APPENDICES

Appendix I: List of Proposed Tables

LIST OF TABLES

Table 1: Summary of Demographic and Baseline Characteristics of Subjects Included in the Multiple Ascending Dose Trial PK Analysis

Note: Racial categories will be expanded as appropriate.

Parameter	Group 1 (3 mg/kg) (N=)	Group 2 (7.5 mg/kg) (N=)	Group 3 (15 mg/kg) (N=)	All Groups (N=)
Sex – N (%)				
Male	x (x)	x (x)	x (x)	x (x)
Female	x (x)	x (x)	x (x)	x (x)
Age (Years)				
Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
Median	x.x	x.x	x.x	x.x
Min, Max	x, x	x, x	x, x	x, x
Height (cm)				
Mean (SD)	x (x.x)	x (x.x)	x (x.x)	x (x.x)
Median	x	x	x	x
Min, Max	x, x	x, x	x, x	x, x
Weight (kg)				
Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
Median	x.x	x.x	x.x	x.x
Min, Max	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
BMI (kg/m^2)				
Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
Median	x.x	x.x	x.x	x.x
Min, Max	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
Race – N (%)				
Black or African American	x (x)	x (x)	x (x)	x (x)
White	x (x)	x (x)	x (x)	x (x)

Table 2: Summary of Demographic and Baseline Characteristics of Subjects Included in the Food Effect Trial PK Analysis

Note: Racial categories will be expanded as appropriate.

Parameter	Group 4, Sequence A (N=)	Group 4, Sequence B (N=)	All Groups (N=)
Sex – N (%)			
Male	x (x)	x (x)	x (x)
Female	x (x)	x (x)	x (x)
Age (Years)			
Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)
Median	x.x	x.x	x.x
Min, Max	x, x	x, x	x, x
Height (cm)			
Mean (SD)	x (x.x)	x (x.x)	x (x.x)
Median	x	x	x
Min, Max	x, x	x, x	x, x
Weight (kg)			
Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)
Median	x.x	x.x	x.x
Min, Max	x.x, x.x	x.x, x.x	x.x, x.x
BMI (kg/m^2)			
Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)
Median	x.x	x.x	x.x
Min, Max	x.x, x.x	x.x, x.x	x.x, x.x
Race – N (%)			
Black or African American	x (x)	x (x)	x (x)
White	x (x)	x (x)	x (x)

Table 3: Individual Concentrations and Summary Statistics by Nominal Time: Group 1 (3 mg/kg), Dose 1

	Nominal Time After Dose 1(hours)									
Subject ID	**Pre-dose**	**0.5**	**1**	**2**	**3**	**4**	**6**	**9**	**12**	**24**
99ZZZ001	x	x	x	x	x	x	x	x	x	x
99ZZZ002	x	x	x	x	x	x	x	x	x	x
99ZZZ003	x	x	x	x	x	x	x	x	x	x
…	x	x	x	x	x	x	x	x	x	x
Statistic										
N[1]	x	x	x	x	x	x	x	x	x	x
Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
SD	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
GM	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
(Min, Max)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)

[1] Number of data points used to compute the summary statistics. BQL values were imputed as 0 if they did not come after a PK sample concentration that is above the LLOQ and treated as missing otherwise.

Table 4: Individual Concentrations and Summary Statistics by Nominal Time: Group 2 (7.5 mg/kg), Dose 1

Table 5: Individual Concentrations and Summary Statistics by Nominal Time: Group 3 (15 mg/kg), Dose 1

Table 4 and **Table 5** will use the form of **Table 3** to display corresponding data for Groups 2 and 3.

Table 6: Individual Concentrations and Summary Statistics by Nominal Time: Group 1 (3 mg/kg), Dose 5

	Nominal Time After Dose 5 (hours)											
Subject ID	**Pre-dose**	**.5**	**1**	**2**	**3**	**4**	**6**	**9**	**12**	**24**	**72**	**120**
99ZZZ001	x	x	x	x	x	x	x	x	x	x	x	x
99ZZZ002	x	x	x	x	x	x	x	x	x	x	x	x
99ZZZ003	x	x	x	x	x	x	x	x	x	x	x	x
…	x	x	x	x	x	x	x	x	x	x	x	x
Statistic												
N[1]	x	x	x	x	x	x	x	x	x	x	x	x
Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
SD	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
GM	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
(Min, Max)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)

[1] Number of data points used to compute the summary statistics. BQL values were imputed as 0 if they did not come after a PK sample concentration that is above the LLOQ and treated as missing otherwise.

Table 7: Individual Concentrations and Summary Statistics by Nominal Time: Group 2 (7.5 mg/kg), Dose 5

Table 8: Individual Concentrations and Summary Statistics by Nominal Time: Group 3 (15 mg/kg), Dose 5

Table 7 and **Table 8** will use the form of **Table 6** to display corresponding data for Group 2 and Group 3.

Table 9: Peak and Trough Concentrations by Dose: Group 1 (3 mg/kg)

	Dose 1		Dose 2		Dose 3		Dose 4		Dose 5	
	Peak[1]	**Trough[2]**	**Peak**	**Trough**	**Peak**	**Trough**	**Peak**	**Trough**	**Peak**	**Trough**
99ZZZ001	x	x	x	x	x	x	x	x	x	x
99ZZZ002	x	x	x	x	x	x	x	x	x	x
99ZZZ003	x	x	x	x	x	x	x	x	x	x
…	x	x	x	x	x	x	x	x	x	x
Statistic										
N[3]	x	x	x	x	x	x	x	x	x	x
Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
SD	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
GM	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
(Min, Max)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)

[1] Peak concentration is shown in this table as concentration at 2 hours (nominal time) after the corresponding dose.
[2] Trough concentration is shown in this table as concentration at 24 hours (nominal time) after the corresponding dose.
[3] Number of data points used to compute the summary statistics. BQL values were imputed as 0 if they did not come after a PK sample concentration that is above the LLOQ and treated as missing otherwise.

Table 10: Peak and Trough Concentrations by Dose: Group 2 (7.5 mg/kg)

Table 11: Peak and Trough Concentrations by Dose: Group 3 (15 mg/kg)

Table 10 and **Table 11** will use the form of **Table 9** to display corresponding data for Group 2 and Group 3.

Table 12: Individual Concentrations and Summary Statistics by Nominal Time: Group 4 Sequence A, Period 1 (3mg/kg, Fasted)

Subject ID	Nominal Time After Dose (hours)									
	Pre-dose	**0.5**	**1**	**2**	**3**	**4**	**6**	**9**	**12**	**24**
99ZZZ001	x	x	x	x	x	x	x	x	x	x
99ZZZ002	x	x	x	x	x	x	x	x	x	x
99ZZZ003	x	x	x	x	x	x	x	x	x	x
…	x	x	x	x	x	x	x	x	x	x
Statistic										
N[1]	x	x	x	x	x	x	x	x	x	x
Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
SD	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
GM	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
(Min, Max)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)

[1] Number of data points used to compute the summary statistics. BQL values were imputed as 0 if they did not come after a PK sample concentration that is above the LLOQ and treated as missing otherwise.

Table 13: Individual Concentrations and Summary Statistics by Nominal Time: Group 4 Sequence A, Period 2 (3mg/kg, Fed)

	Nominal Time After Dose (hours)										
Subject ID	**Pre-dose**	**.5**	**1**	**2**	**3**	**4**	**6**	**9**	**12**	**24**	**144**
99ZZZ001	x	x	x	x	x	x	x	x	x	x	x
99ZZZ002	x	x	x	x	x	x	x	x	x	x	x
99ZZZ003	x	x	x	x	x	x	x	x	x	x	x
…	x	x	x	x	x	x	x	x	x	x	x
Statistics											
N[1]	x	x	x	x	x	x	x	x	x	x	x
Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
SD	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
GM	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
(Min, Max)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)

[1] Number of data points used to compute the summary statistics. BQL values were imputed as 0 if they did not come after a PK sample concentration that is above the LLOQ and treated as missing otherwise.

Table 14: Individual Concentrations and Summary Statistics by Nominal Time: Group 4 Sequence B, Period 1 (3mg/kg, Fed)

Table 15: Individual Concentrations and Summary Statistics by Nominal Time: Group 4 Sequence B, Period 2 (3mg/kg, Fasted)

Table 14 and **Table 15** will use the forms of **Table 12** and **Table 13** to display corresponding data for Group 4, Sequence B.

Table 16: Individual PK Parameters and Summary Statistics: Group 1 (3 mg/kg), Dose 1

Subject ID	AUC_τ (ng·hr/mL)	T_{max} (hr)	C_{max} (ng/mL)	C_{trough} (ng/mL)	λ_z (hr^{-1})	$t_{1/2}$ (hr)
99ZZZ001	x	x.x	x	x	x.x	x.x
99ZZZ002	x	x.x	x	x	x.x	x.x
99ZZZ003	x	x.x	x	x	x.x	x.x
…						
Statistic						
N[1]	x	x	x	x	x	x
Mean	x.x	x.x	x.x	x.x	x.x	x.x
SD	x.x	x.x	x.x	x.x	x.x	x.x
Min	x	x.x	x	x	x.x	x.x
Median	x	x.x	x	x	x.x	x.x
Max	x	x.x	x	x	x.x	x.x
CV %	x	x	x	x	x	x
GM	x.x	x.x	x.x	x.x	x.x	x.x

[1] Number of data points used to compute the summary statistics. BQL values were imputed as 0 if they did not come after a PK sample concentration that is above the LLOQ and treated as missing otherwise.

Table 17: Individual PK Parameters and Summary Statistics: Group 1 (3 mg/kg), Dose 5

Subject ID	AUC_{τ} (ng·hr/mL)	AUC_{last} (ng·hr/mL)	T_{max} (hr)	C_{max} (ng/mL)	C_{trough} (ng/mL)	$t_{1/2}$ (hr)	CL_{ss}/F (L/hr/kg)
99ZZZ001	x	x	x.x	x	x	x.x	x.x
99ZZZ002	x	x	x.x	x	x	x.x	x.x
99ZZZ003	x	x	x.x	x	x	x.x	x.x
…							
Statistic							
N[1]	x	x	x	x	x	x	x
Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x
SD	x.x	x.x	x.x	x.x	x.x	x.x	x.x
Min	x	x	x.x	x	x	x.x	x
Median	x	x	x.x	x	x	x.x	x
Max	x	x	x.x	x	x	x.x	x
CV %	x	x	x	x	x	x	x
GM	x.x	x.x	x.x	x.x	x.x	x.x	x.x

[1] Number of data points used to compute the summary statistics. BQL values were imputed as 0 if they did not come after a PK sample concentration that is above the LLOQ and treated as missing otherwise.

Table 18: Individual PK Parameters and Summary Statistics: Group 2 (7.5 mg/kg), Dose 1

Table 19: Individual PK Parameters and Summary Statistics: Group 2 (7.5 mg/kg), Dose 5

Table 20: Individual PK Parameters and Summary Statistics: Group 3 (15 mg/kg), Dose 1

Table 21: Individual PK Parameters and Summary Statistics: Group 3 (15 mg/kg), Dose 5

Table 18, Table 19, Table 20, and **Table 21** will use the forms of **Table 16 and Table 17** to display corresponding data for Groups 2 and 3.

Table 22: Individual PK Parameters and Summary Statistics: Group 4

Subject ID	AUC_{last} (ng·hr/mL)		$AUC_{0-\infty}$ (ng·hr/mL)		T_{max} (hr)		C_{max} (ng/mL)		$t_{1/2}$ (hr)		CL/F (L/hr/kg)		V_d/F (L/kg)	
	Fed	Fasted	Fed	Fasted	Fed	Fasted	Fed	Fasted	Fed	Fasted	Fed	Fasted	Fed	Fasted
99ZZZ001	x	x	x	x	x.x	x.x	x	x	x.x	x.x	x.x	x.x	x.x	x.x
99ZZZ002	x	x	x	x	x.x	x.x	x	x	x.x	x.x	x.x	x.x	x.x	x.x
99ZZZ003	x	x	x	x	x.x	x.x	x	x	x.x	x.x	x.x	x.x	x.x	x.x
…														
Statistic														
N[1]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
SD	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
Min	x	x	x	x	x.x	x.x	x	x	x.x	x.x	x.x	x.x	x.x	x.x
Median	x	x	x	x	x.x	x.x	x	x	x.x	x.x	x.x	x.x	x.x	x.x
Max	x	x	x	x	x.x	x.x	x	x	x.x	x.x	x.x	x.x	x.x	x.x
CV %	x	x	x	x	x	x	x	x	x	x	x	x	x	x
GM	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x

[1] Number of data points used to compute the summary statistics. BQL values were imputed as 0 if they did not come after a PK sample concentration that is above the LLOQ and treated as missing otherwise.

Table 23: Summary Statistics of PK Parameters by Group and Sex: Groups 1, 2 and 3, Dose 1

Statistics	AUC_τ (ng·hr/mL)		T_{max} (hr)		C_{max} (ng/mL)		C_{trough} (ng/mL)		$t_{1/2}$ (hr)	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Group 1										
N[1]	x	x	x	x	x	x	x	x	x	x
Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
SD	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
Min	x	x	x.x	x.x	x	x	x	x	x.x	x.x
Median	x	x	x.x	x.x	x	x	x	x	x.x	x.x
Max	x	x	x.x	x.x	x	x	x	x	x.x	x.x
CV %	x	x	x	x	x	x	x	x	x	x
GM	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
Group 2										
N[1]	x	x	x	x	x	x	x	x	x	x
Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
SD	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
Min	x	x	x.x	x.x	x	x	x	x	x.x	x.x
Median	x	x	x.x	x.x	x	x	x	x	x.x	x.x
Max	x	x	x.x	x.x	x	x	x	x	x.x	x.x
CV %	x	x	x	x	x	x	x	x	x	x
GM	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
Group 3										
N[1]	x	x	x	x	x	x	x	x	x	x
Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
SD	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
Min	x	x	x.x	x.x	x	x	x	x	x.x	x.x
Median	x	x	x.x	x.x	x	x	x	x	x.x	x.x
Max	x	x	x.x	x.x	x	x	x	x	x.x	x.x
CV %	x	x	x	x	x	x	x	x	x	x
GM	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x

[1] Number of data points used to compute the summary statistics. BQL values were imputed as 0 if they did not come after a PK sample concentration that is above the LLOQ and treated as missing otherwise.

Table 24: Summary Statistics of PK Parameters by Group and Sex: Groups 1, 2 and 3, Dose 5

Statistics	AUC_τ (ng·hr/mL)		T_{max} (hr)		C_{max} (ng/mL)		C_{trough} (ng/mL)		$t_{1/2}$ (hr)	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Group 1										
N[1]	x	x	x	x	x	x	x	x	x	x
Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
SD	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
Min	x	x	x.x	x.x	x	x	x	x	x.x	x.x
Median	x	x	x.x	x.x	x	x	x	x	x.x	x.x
Max	x	x	x.x	x.x	x	x	x	x	x.x	x.x
CV %	x	x	x	x	x	x	x	x	x	x
GM	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
Group 2										
N[1]	x	x	x	x	x	x	x	x	x	x
Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
SD	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
Min	x	x	x.x	x.x	x	x	x	x	x.x	x.x
Median	x	x	x.x	x.x	x	x	x	x	x.x	x.x
Max	x	x	x.x	x.x	x	x	x	x	x.x	x.x
CV %	x	x	x	x	x	x	x	x	x	x
GM	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
Group 3										
N[1]	x	x	x	x	x	x	x	x	x	x
Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
SD	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
Min	x	x	x.x	x.x	x	x	x	x	x.x	x.x
Median	x	x	x.x	x.x	x	x	x	x	x.x	x.x
Max	x	x	x.x	x.x	x	x	x	x	x.x	x.x
CV %	x	x	x	x	x	x	x	x	x	x
GM	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x

[1] Number of data points used to compute the summary statistics. BQL values were imputed as 0 if they did not come after a PK sample concentration that is above the LLOQ and treated as missing otherwise.

Table 25: Summary Statistics of PK Parameters by Group and Sex: Group 4

Statistics	AUC_{last} (ng·hr/mL)		T_{max} (hr)		C_{max} (ng/mL)		$t_{1/2}$ (hr)	
	Male	Female	Male	Female	Male	Female	Male	Female
Fed								
N[1]	x	x	x	x	x	x	x	x
Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
SD	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
Min	x	x	x.x	x.x	x	x	x.x	x.x
Median	x	x	x.x	x.x	x	x	x.x	x.x
Max	x	x	x.x	x.x	x	x	x.x	x.x
CV %	x	x	x	x	x	x	x	x
GM	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
Fasted								
N[1]	x	x	x	x	x	x	x	x
Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
SD	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
Min	x	x	x.x	x.x	x	x	x.x	x.x
Median	x	x	x.x	x.x	x	x	x.x	x.x
Max	x	x	x.x	x.x	x	x	x.x	x.x
CV %	x	x	x	x	x	x	x	x
GM	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x

[1] Number of data points used to compute the summary statistics. BQL values were imputed as 0 if they did not come after a PK sample concentration that is above the LLOQ and treated as missing otherwise.

Table 26: Statistical Analysis of Attainment of Steady State

Exposure Parameter	Dose Level	Day 3 vs. Day 5 Comparison[1]		Day 4 vs. Day 5 Comparison[1]	
		Geometric Mean Ratio (95% CI)	p-value	Geometric Mean Ratio (95% CI)	p-value
C_{max} (ng/mL)	3 mg/kg	x.xxx (x.xxx, x.xxx)	x.xxx	x.xxx (x.xxx, x.xxx)	x.xxx
	7.5 mg/kg	x.xxx (x.xxx, x.xxx)	x.xxx	x.xxx (x.xxx, x.xxx)	x.xxx
	15 mg/kg	x.xxx (x.xxx, x.xxx)	x.xxx	x.xxx (x.xxx, x.xxx)	x.xxx
C_{trough}(ng/mL)	3 mg/kg	x.xxx (x.xxx, x.xxx)	x.xxx	x.xxx (x.xxx, x.xxx)	x.xxx
	7.5 mg/kg	x.xxx (x.xxx, x.xxx)	x.xxx	x.xxx (x.xxx, x.xxx)	x.xxx
	15 mg/kg	x.xxx (x.xxx, x.xxx)	x.xxx	x.xxx (x.xxx, x.xxx)	x.xxx

[1] Based on a mixed effects model with fixed effects of day, dose group, and day*dose group interaction, and random effect of subject.

Table 27: Population Summary Statistics for Accumulation Ratio

AR Estimation Method		Group 1 (3 mg/kg)	Group 2 (7.5 mg/kg)	Group 3 (15 mg/kg)
$AR = \frac{AUC_{\tau,\ Dose\ 5}}{AUC_{\tau,\ Dose\ 1}}$	N	x	x	x
	Mean	x.x	x.x	x.x
	SD	x.x	x.x	x.x
	Min	x.x	x.x	x.x
	Median	x.x	x.x	x.x
	Max	x.x	x.x	x.x
	CV %	x	x	x
	GM	x.x	x.x	x.x
$AR = \frac{C_{max,\ Dose\ 5}}{C_{max,\ Dose\ 1}}$	N	x	x	x
	Mean	x.x	x.x	x.x
	SD	x.x	x.x	x.x
	Min	x.x	x.x	x.x
	Median	x.x	x.x	x.x
	Max	x.x	x.x	x.x
	CV %	x	x	x
	GM	x.x	x.x	x.x
$AR = \frac{1}{1-e^{-\lambda_Z \tau}}$	N	x	x	x
	Mean	x.x	x.x	x.x
	SD	x.x	x.x	x.x
	Min	x.x	x.x	x.x
	Median	x.x	x.x	x.x
	Max	x.x	x.x	x.x
	CV %	x	x	x
	GM	x.x	x.x	x.x

Note: λ_Z from Dose 5 is used to estimate AR.

Table 28: Dose Proportionality Power Model Estimates: Groups 1-3

	Exposure Parameter	$\widehat{\beta}$	90% CI	Conclusion[1]
Dose 1	C_{max} (ng/mL)	x.xxx	(x.xxx, x.xxx)	Proportional
	C_{trough} (ng/mL)	x.xxx	(x.xxx, x.xxx)	Proportional
	AUC_{τ} $(ng \cdot \frac{hr}{mL})$	x.xxx	(x.xxx, x.xxx)	Proportional
Dose 5	C_{max} (ng/mL)	x.xxx	(x.xxx, x.xxx)	Not Proportional
	C_{trough} (ng/mL)	x.xxx	(x.xxx, x.xxx)	Not Proportional
	AUC_{τ} $(ng \cdot \frac{hr}{mL})$	x.xxx	(x.xxx, x.xxx)	Inconclusive

[1]Based on comparison of 90% CI to limits of (x.xxx, x.xxx) in accordance with FDA-recommended bioequivalence criteria

Table 29: Geometric Mean Dose-adjusted Exposure by Dose Group

		Geometric Mean of Dose-adjusted Exposure (95% CI)		
	Exposure Parameter	**Group 1 (3 mg/kg)**	**Group 2 (7.5 mg/kg)**	**Group 3 (15 mg/kg)**
Dose 1	$C_{max}\left(\frac{ng/mL}{mg/kg}\right)$	x.x	x.x	x.x
		x.x	x.x	x.x
		x.x	x.x	x.x
	$C_{trough}\left(\frac{ng/mL}{mg/kg}\right)$	x.x	x.x	x.x
		x.x	x.x	x.x
		x.x	x.x	x.x
	$AUC_{\tau}\left(\frac{ng \cdot hr/mL}{mg/kg}\right)$	x.x	x.x	x.x
		x.x	x.x	x.x
		x.x	x.x	x.x
Dose 5	$C_{max}\left(\frac{ng/mL}{mg/kg}\right)$	x.x	x.x	x.x
		x.x	x.x	x.x
		x.x	x.x	x.x
	$C_{trough}\left(\frac{ng/mL}{mg/kg}\right)$	x.x	x.x	x.x
		x.x	x.x	x.x
		x.x	x.x	x.x
	$AUC_{\tau}\left(\frac{ng \cdot hr/mL}{mg/kg}\right)$	x.x	x.x	x.x
		x.x	x.x	x.x
		x.x	x.x	x.x

Table 30: Summary of Shift in T_{max} following Multiple Dosing

	Median T_{max} (hr)		Estimated Median Difference (hr)	90% CI of Estimated Median Difference (hr)
	Dose 1	Dose 5		
Group 1 (3 mg/kg)	x.x	x.x	x.x	x.x, x.x
Group 2 (7.5 mg/kg)	x.x	x.x	x.x	x.x, x.x
Group 3 (15 mg/kg)	x.x	x.x	x.x	x.x, x.x

Table 31: Statistical Analysis of Food Effect on Exposure

Parameter	Fed GM	Fasted GM	Ratio (Fed / Fasted)	90% CI of Ratio	CV_W (%)
AUC_τ	x.x	x.x	x.xxx	(x.xxx, x.xxx)	xx.xx
$AUC_{(0-\infty)}$	x.x	x.x	x.xxx	(x.xxx, x.xxx)	xx.xx
C_{max}	x.x	x.x	x.xxx	(x.xxx, x.xxx)	xx.xx

Table 32: Statistical Analysis of Food Effect on T_{max}

	Fed Median	Fasted Median	Estimated Median Difference	90% CI of Estimated Median Difference	Wilcoxon Signed Rank Test P-Value
T_{max}	x.x	x.x	x.xxx	(x.xxx, x.xxx)	x.xxx

Appendix II: List of Proposed Figures

LIST OF FIGURES

Figure 1: Concentration Profiles for All Subjects, Groups 1-3

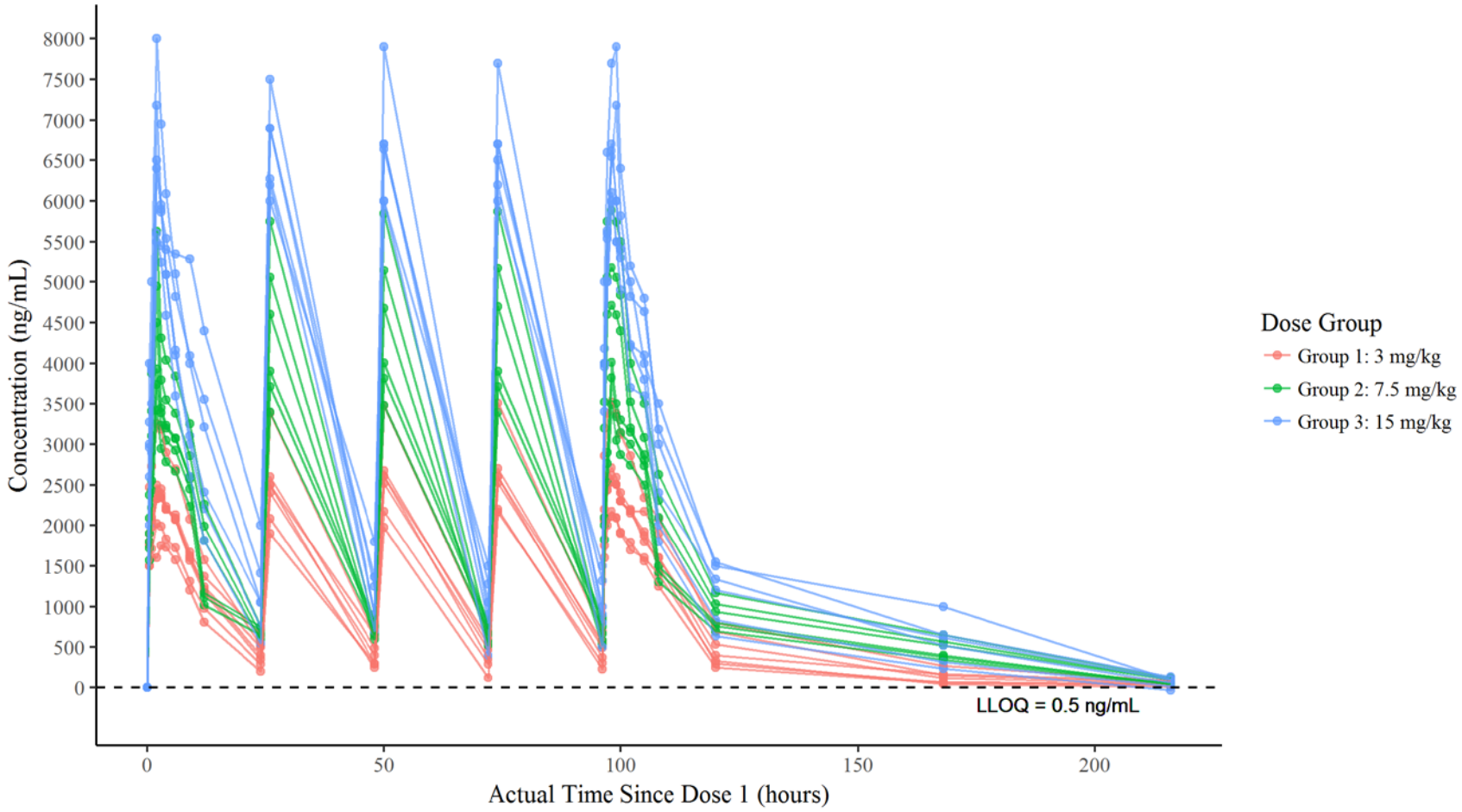


Figure 2: Semi-log Concentration Profiles for All Subjects, Groups 1-3

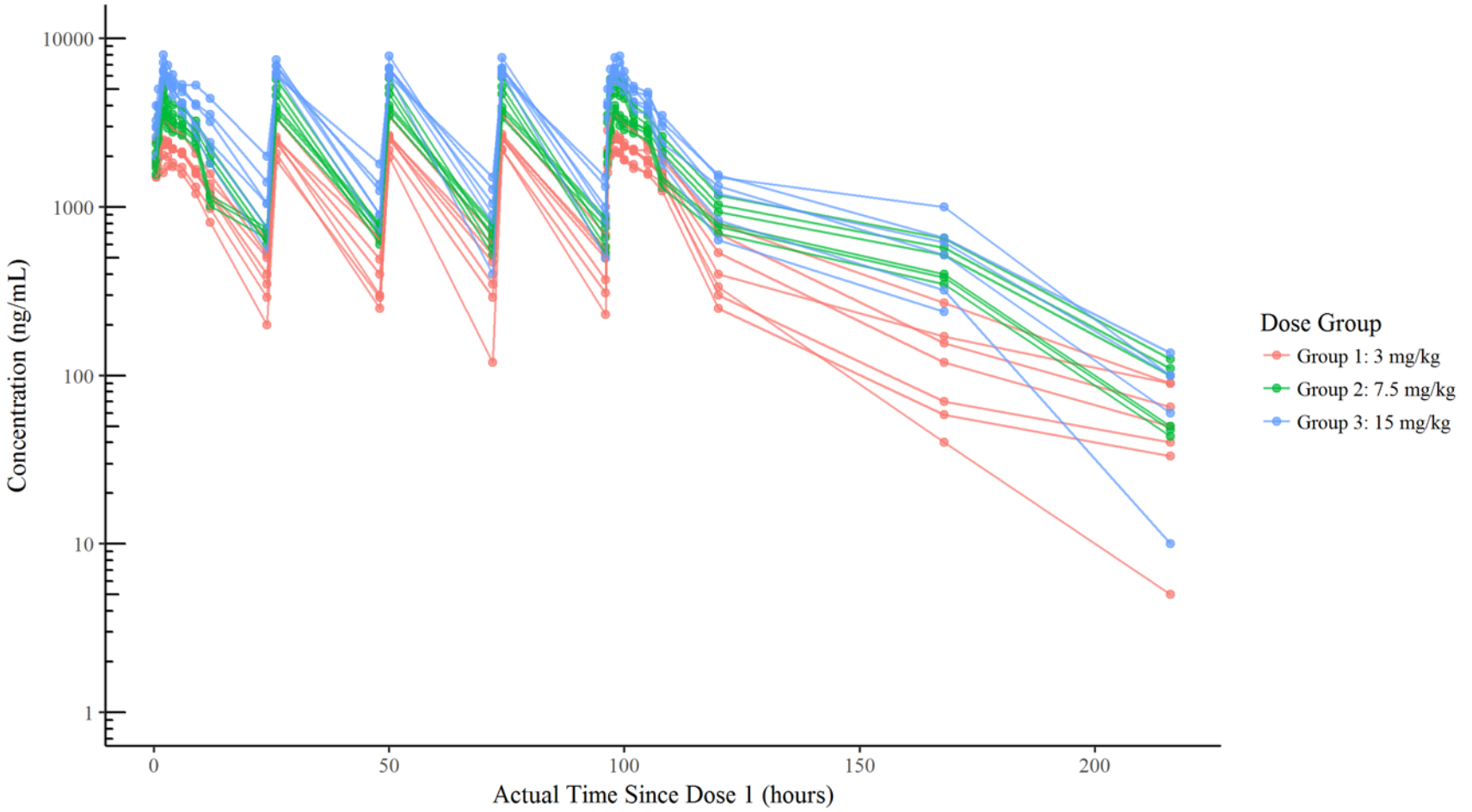
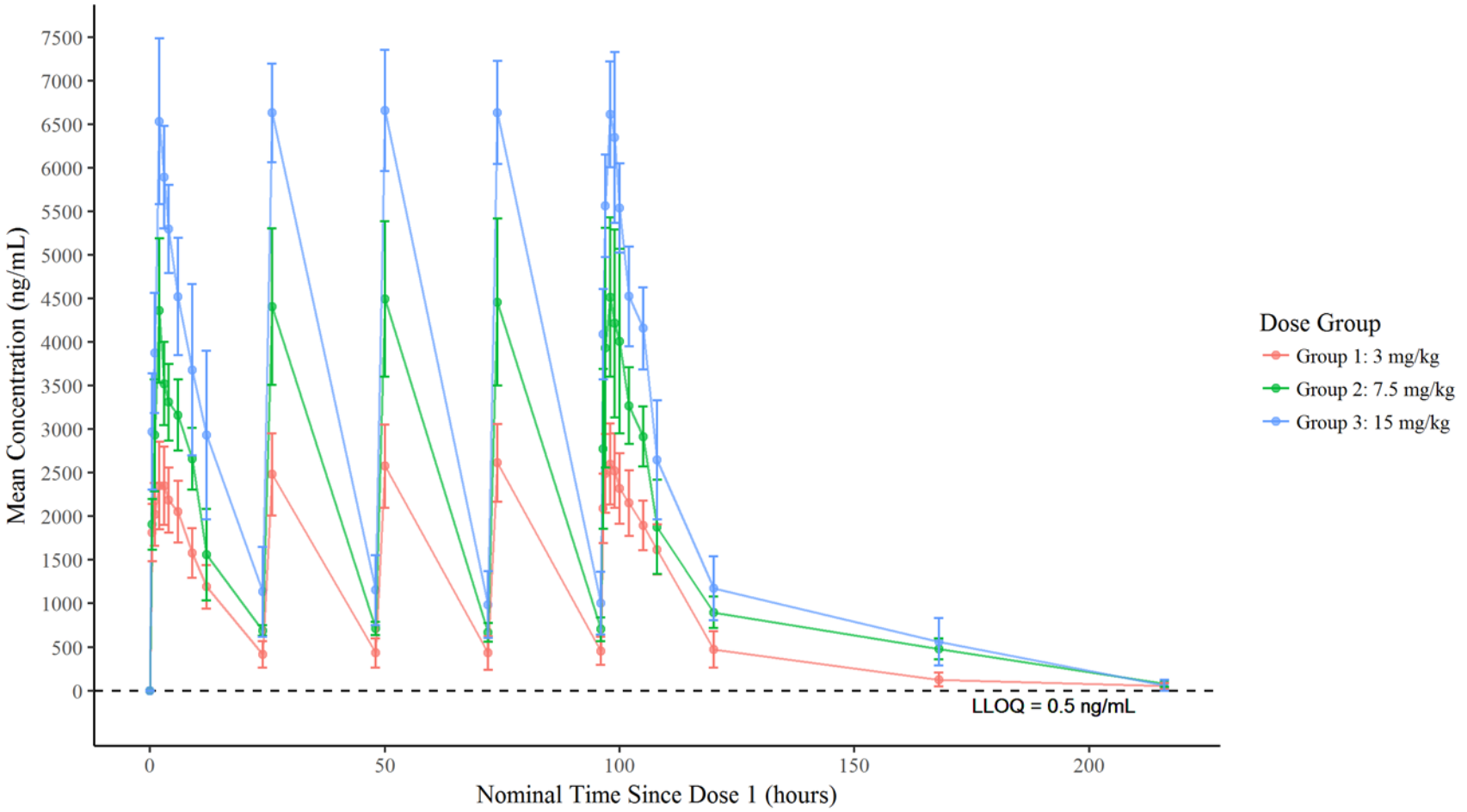
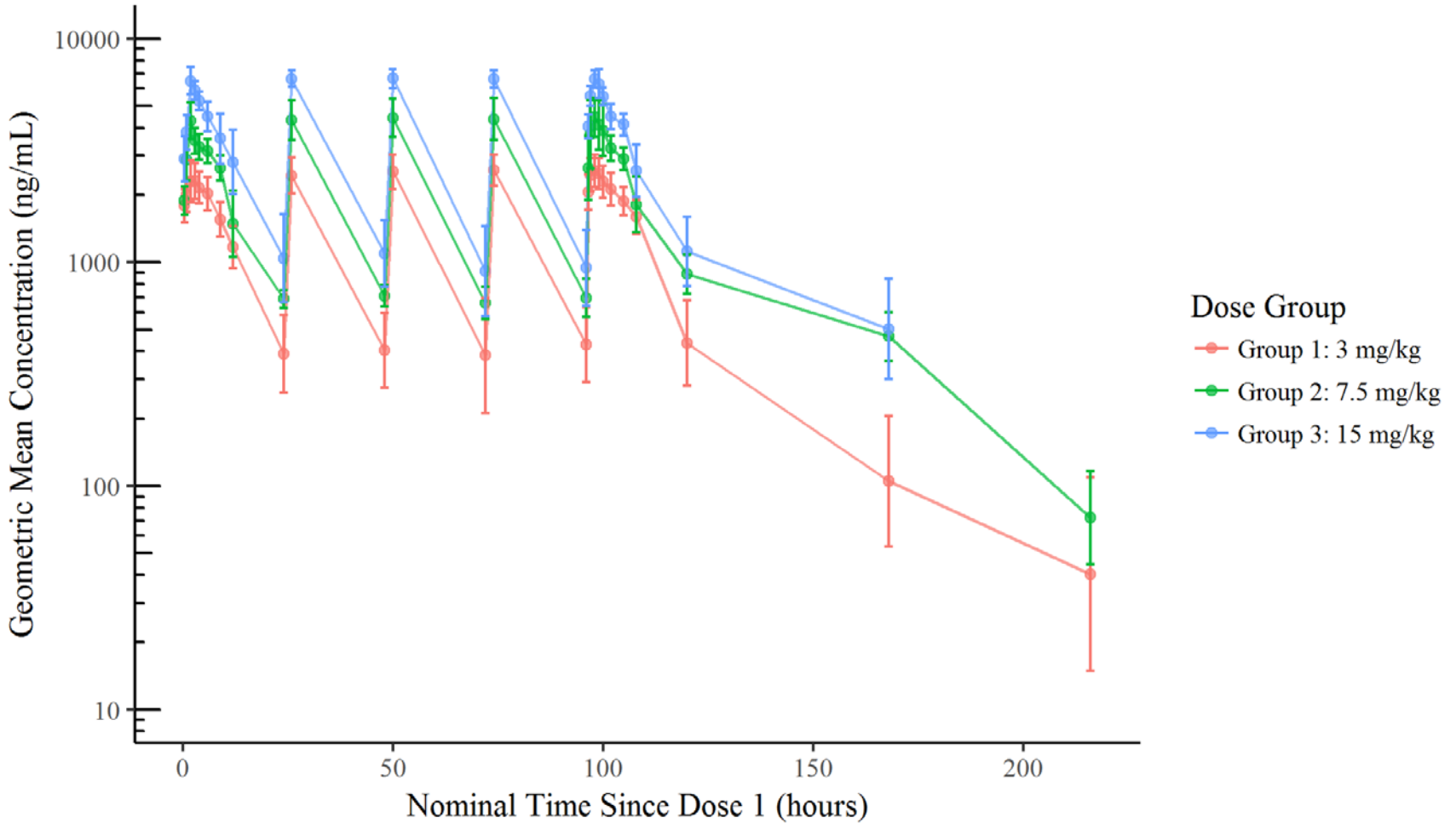


Figure 3: Mean Concentration Profiles, Groups 1-3



Note: Error bars show 1 standard deviation.

Figure 4: Semi-log Geometric Mean Concentration Profiles, Groups 1-3



Note: Error bars show 1 geometric standard deviation.

Figure 5: Subject Concentration Profile by Time, Group 1, Subject 99ZZZ001

The following figure will be repeated for each subject in Groups 1-3.

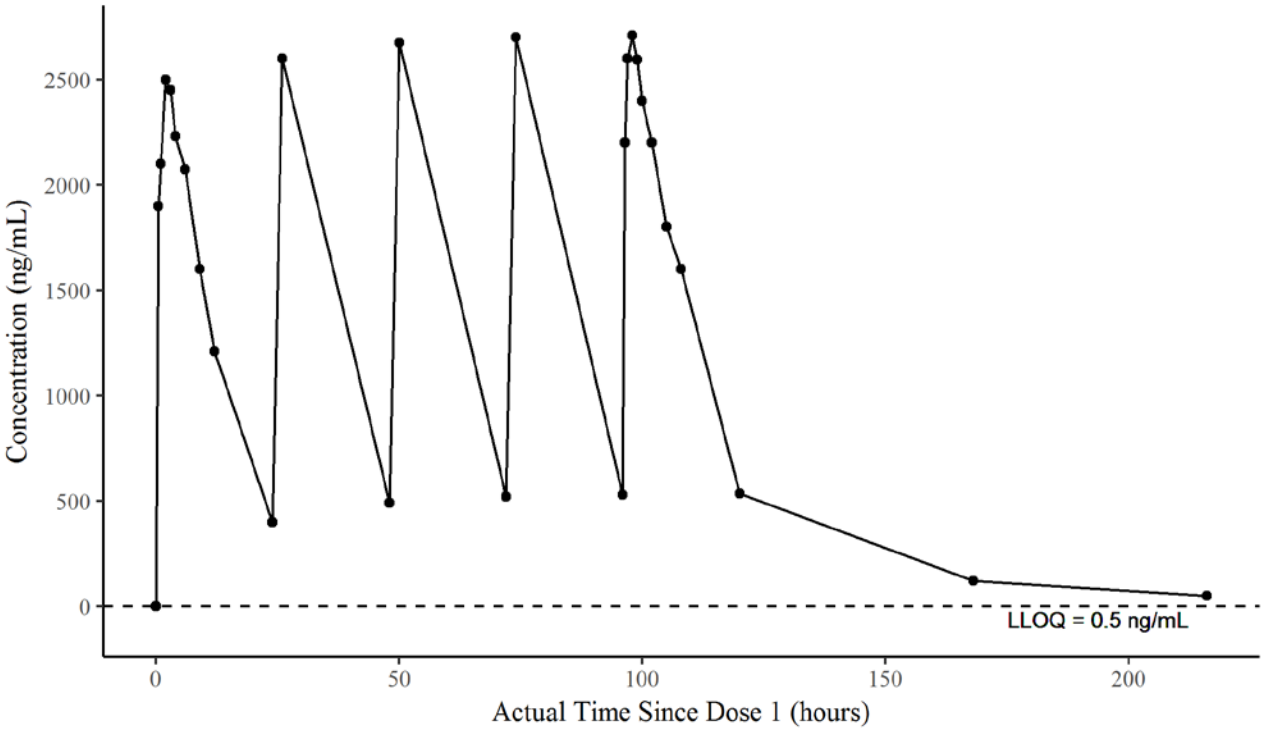


Figure 6: Semi-log Plot of Concentration by Nominal Time, Group 1, Subject 99ZZZ001

The following figure will be repeated for each subject in Groups 1-3.

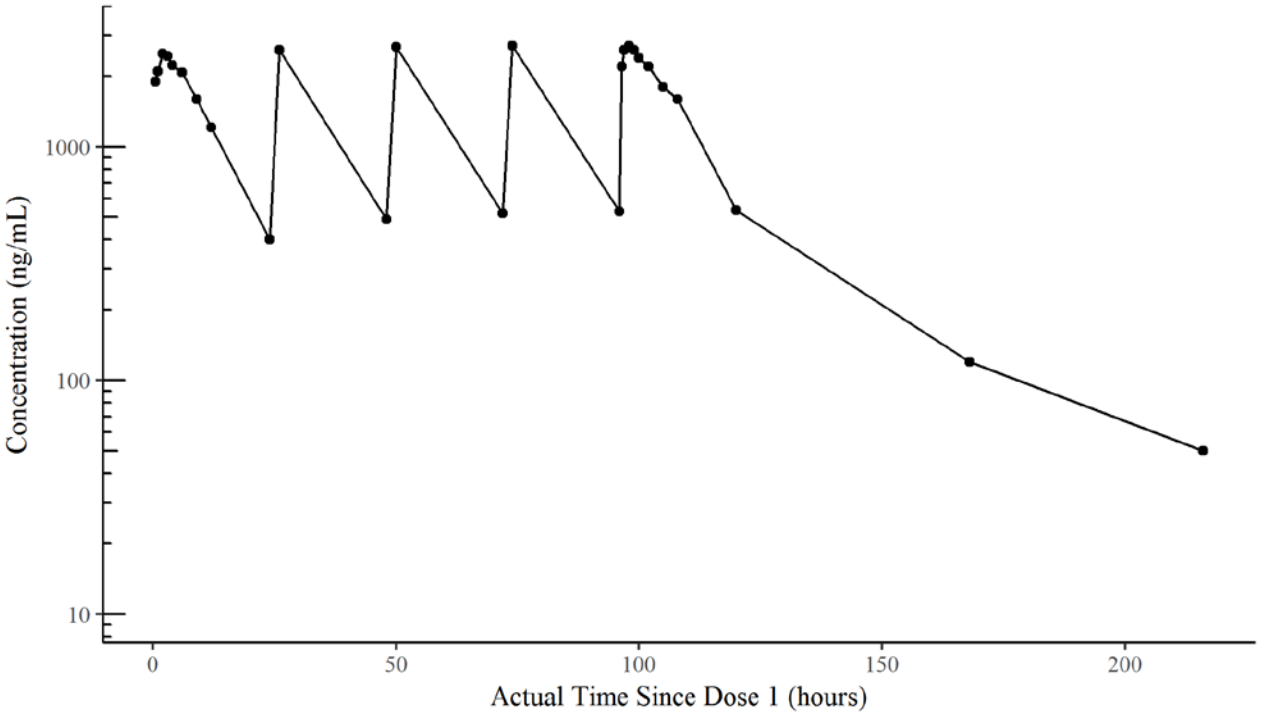


Figure 7: Concentration Profiles for Group 4 by Sequence and Period

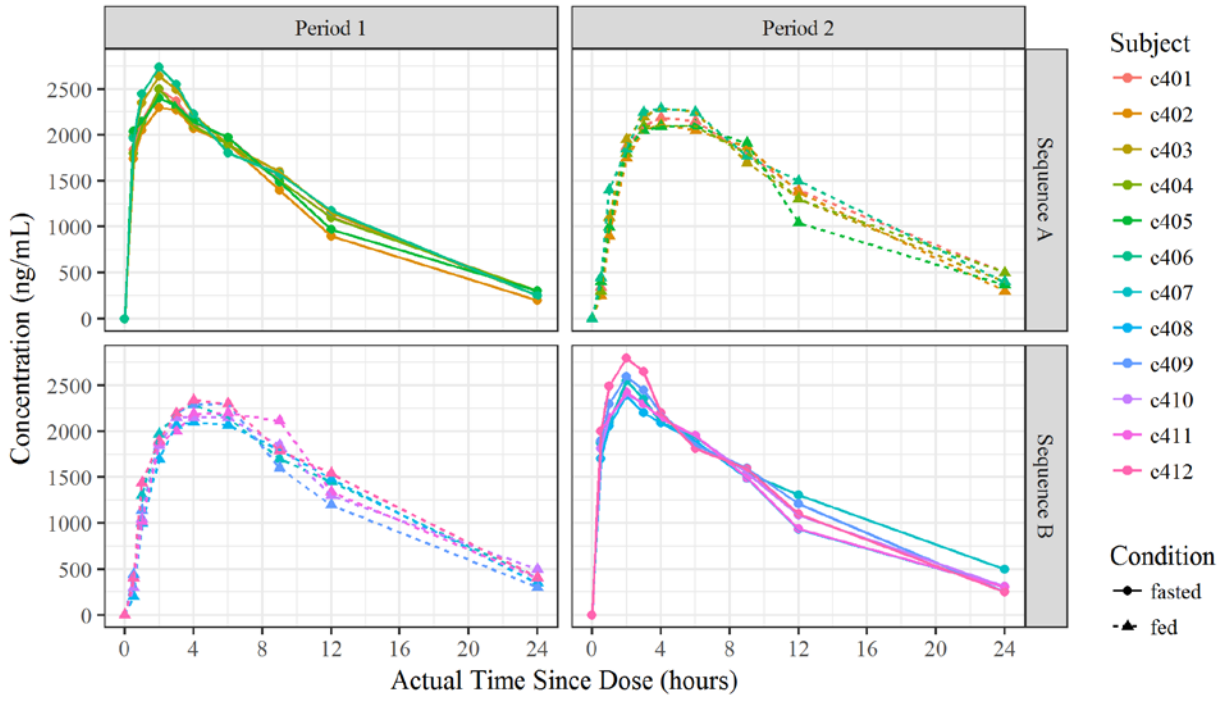


Figure 8: Semi-log Concentration Profiles for Group 4 by Sequence and Period

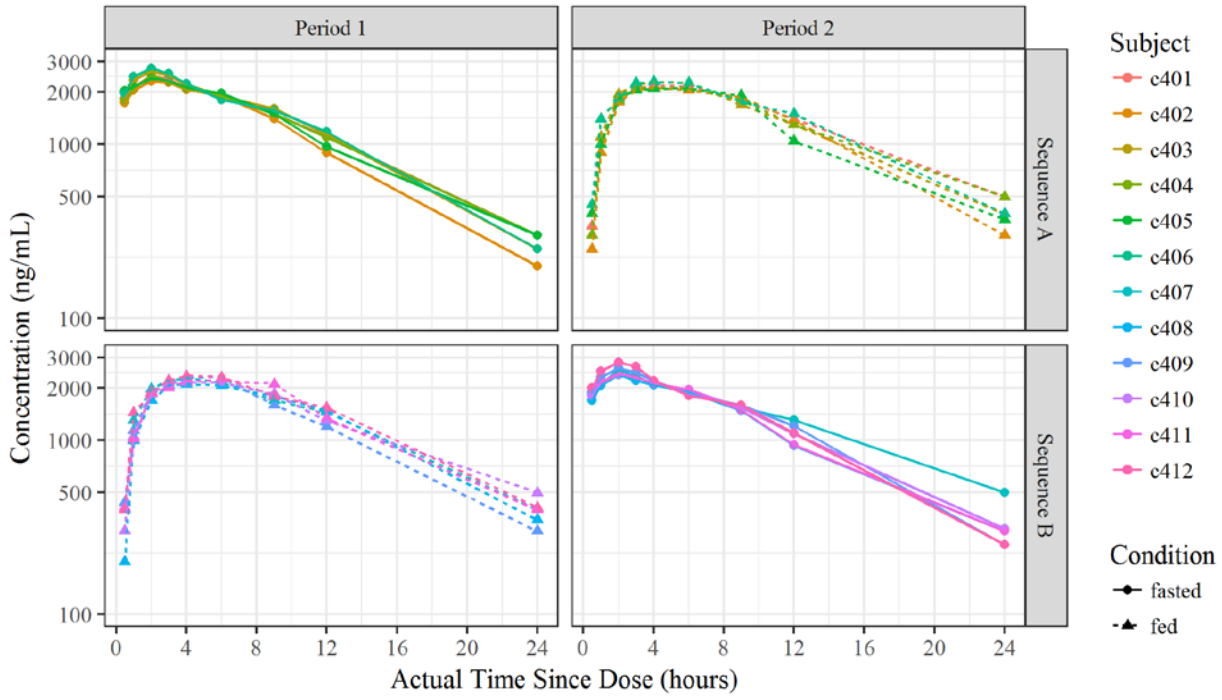
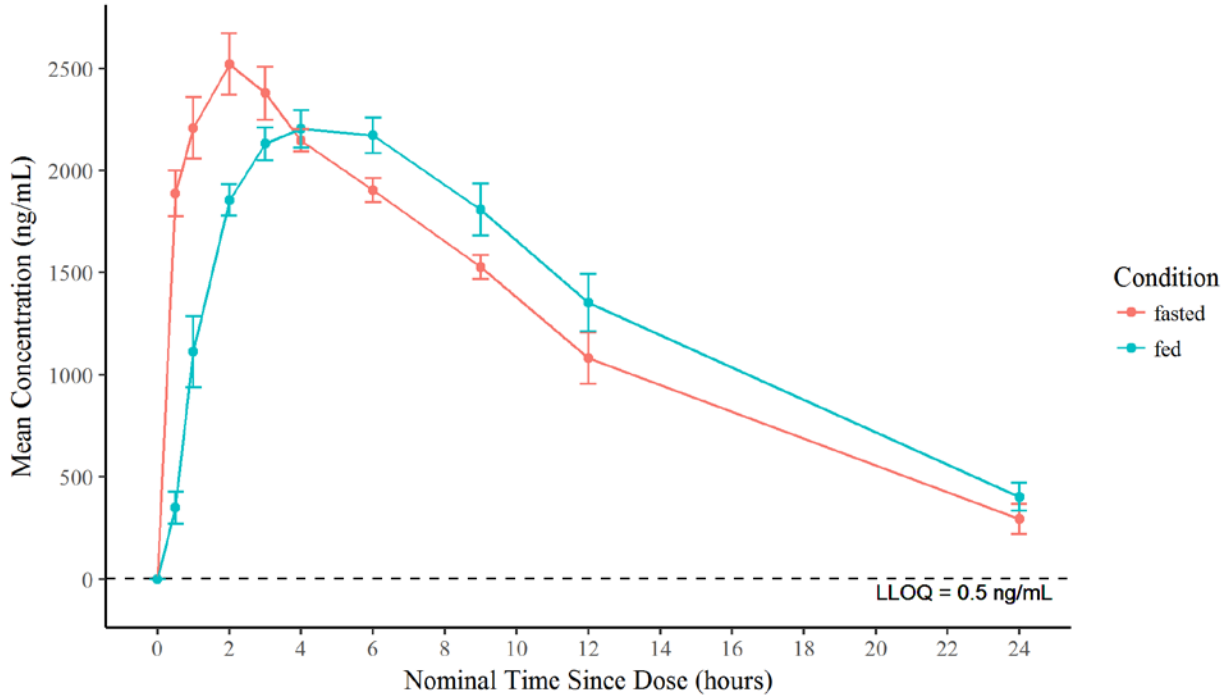
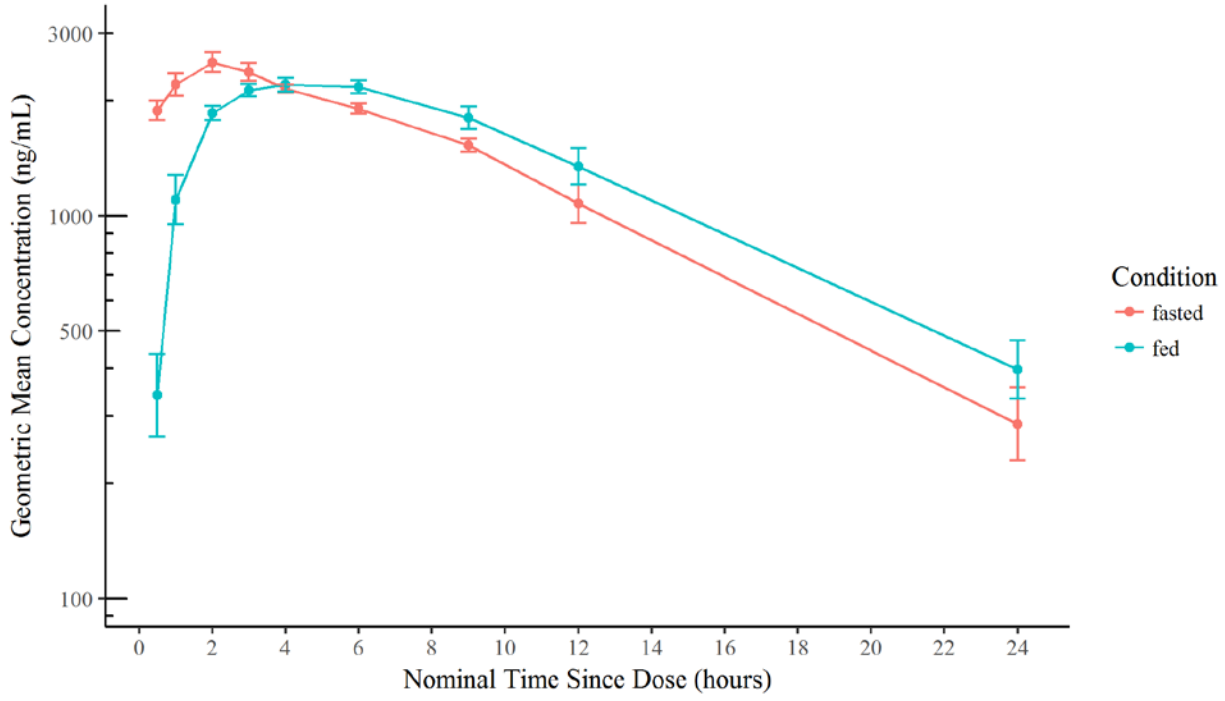


Figure 9: Mean Concentration Profile, Group 4



Note: Error bars show 1 standard deviation.

Figure 10: Semi-log Geometric Mean Concentration Profile, Group 4



Note: Error bars show 1 geometric standard deviation.

Figure 11: Subject Concentration Profile by Time, Group 4, Subject 99ZZZ001

The following figure will be repeated for each subject in Group 4.

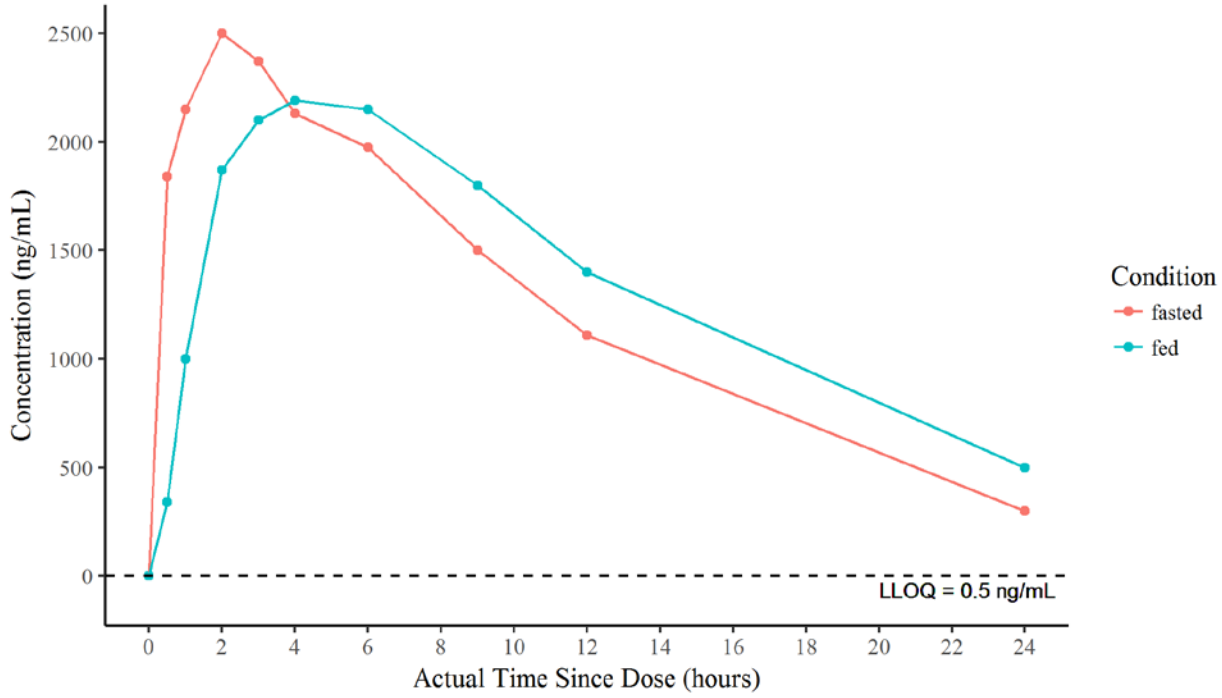


Figure 12: Semi-log Subject Concentration Profile by Time, Group 4, Subject 99ZZZ001

The following figure will be repeated for each subject in Group 4.

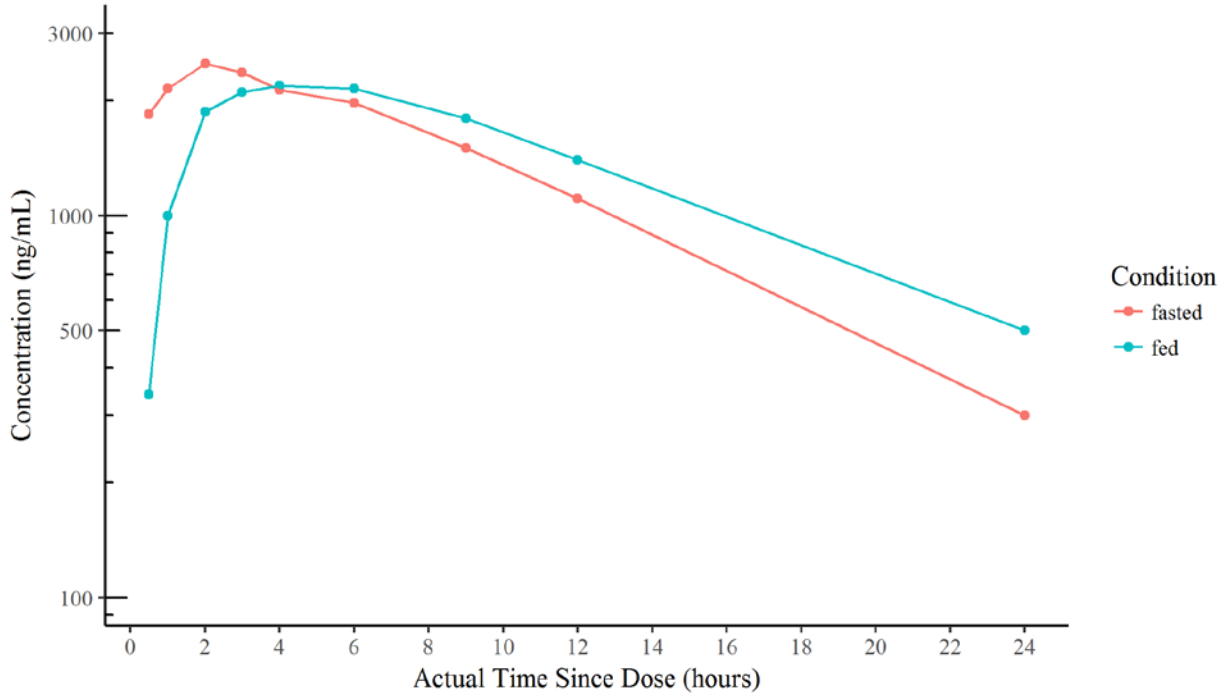


Figure 13: PK Parameters by Dose Number and Sex, Group 1

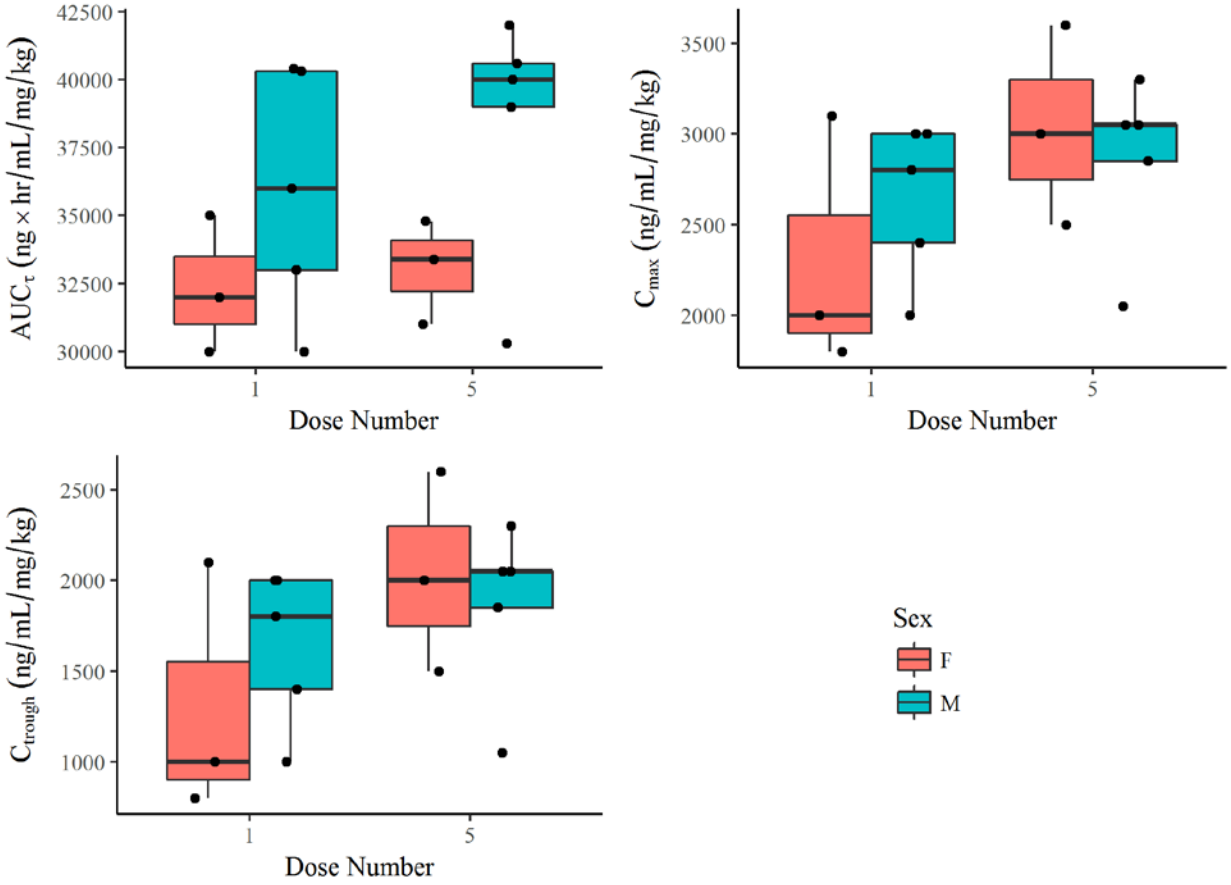


Figure 14: PK Parameters by Dose Number and Sex, Group 2

Figure 15: PK Parameters by Dose Number and Sex, Group 3

Figure 14 and **Figure 15** will use the form of **Figure 13** to present analogous data for Group 2 and Group 3.

Figure 16: PK Parameters by Condition and Sex, Group 4

Figure 16 will use the form of **Figure 13** to present AUC_{last} and C_{max} by fed/fasted condition instead of dose number for Group 4.

Figure 17: PK Parameters by Weight, Dose Number, and Sex, Group 1

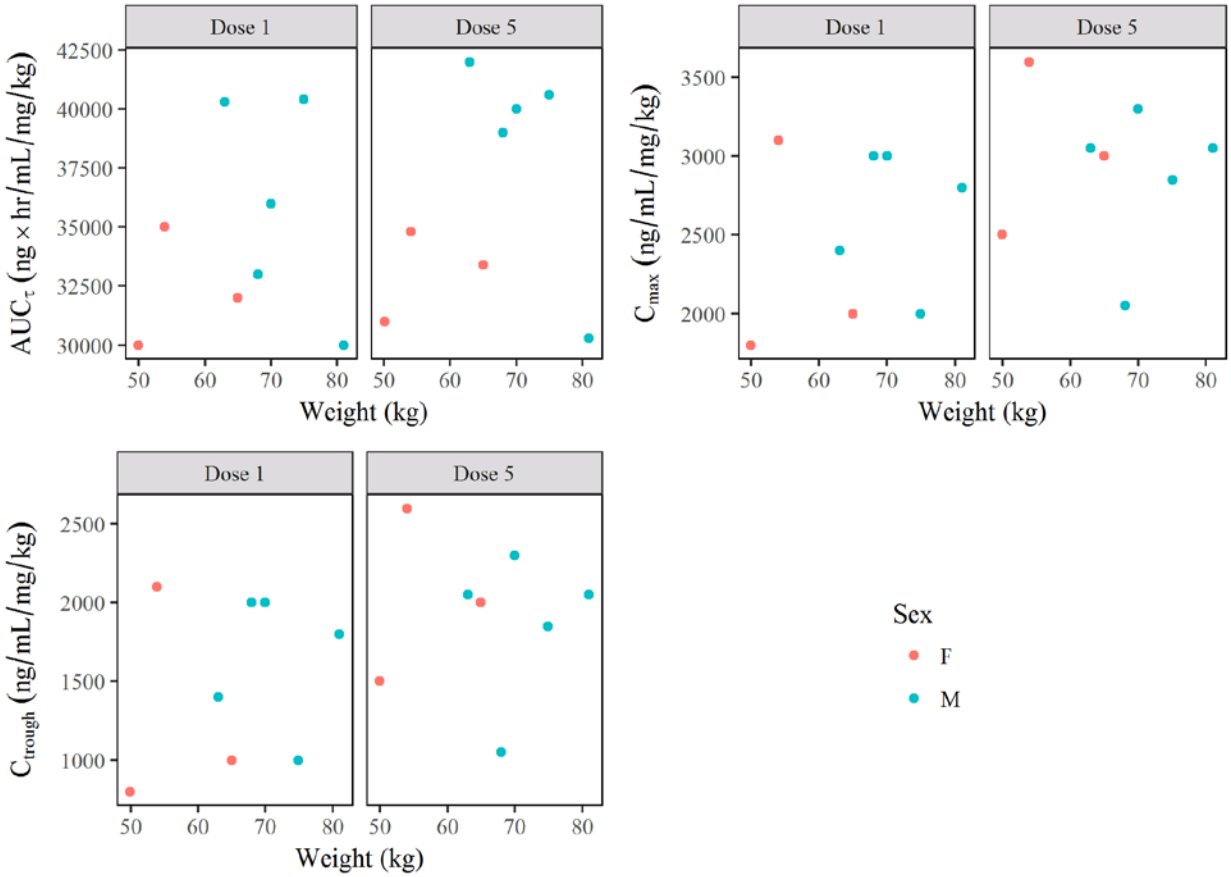


Figure 18: PK Parameters by Weight, Dose Number, and Sex, Group 2

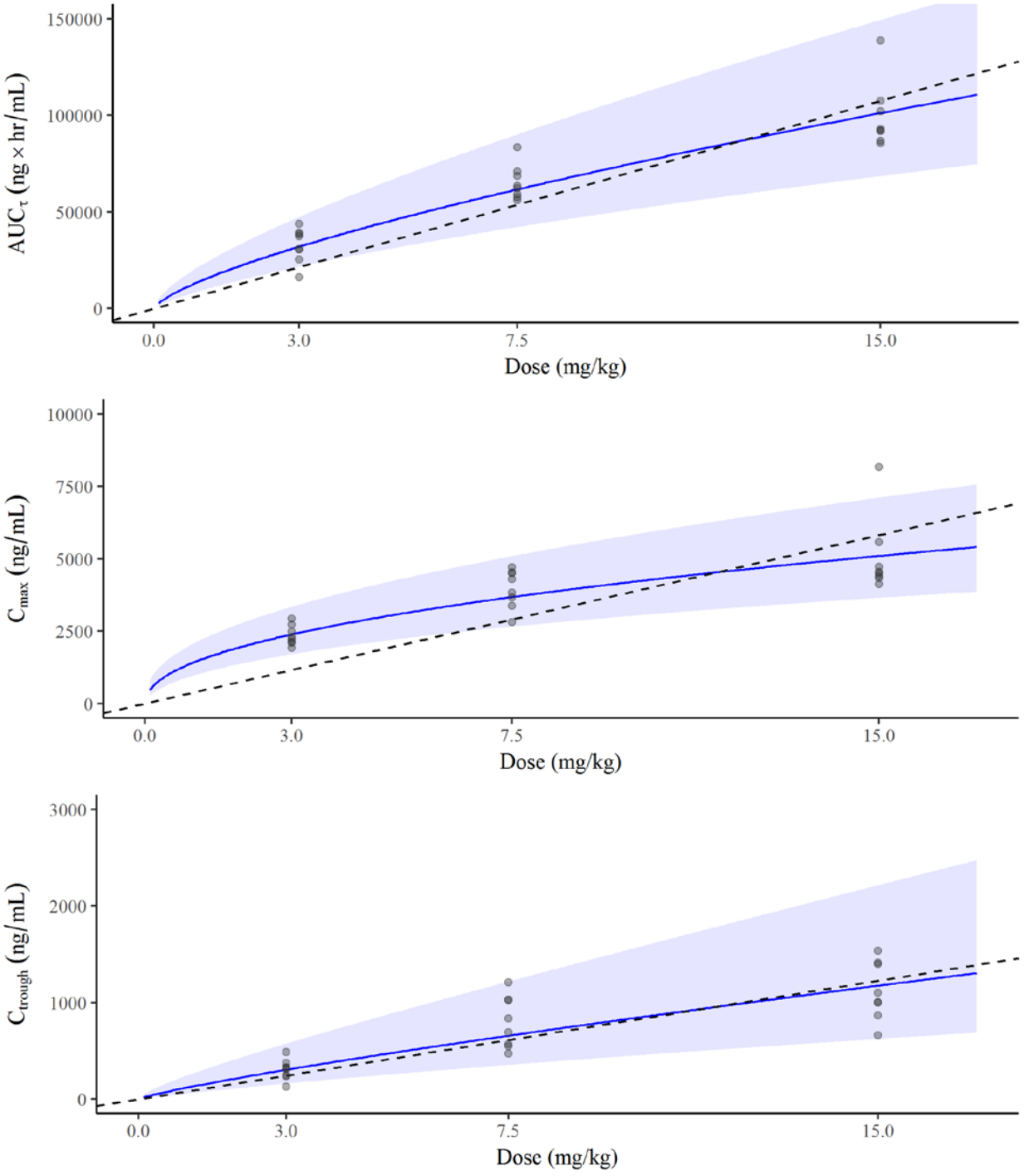
Figure 19: PK Parameters by Weight, Dose Number, and Sex, Group 3

Figure 18 and **Figure 19** will use the form of **Figure 17** to present analogous data for Group 2 and Group 3.

Figure 20: PK Parameters by Weight, Condition, and Sex, Group 4

Figure 20 will use the form of **Figure 17** to present AUC_{last} and C_{max} by fed/fasted condition instead of dose number for Group 4.

Figure 21: Oxfendazole Exposure by Dose, Groups 1-3, Dose 1



Note: Blue line represents predicted values from power model. Blue region shows 90% pointwise prediction interval around the power model curve. Black dashed line shows the best fit straight line through the origin.

Figure 22: Oxfendazole Exposure by Dose, Groups 1-3, Dose 5

This figure will use the form of **Figure 21** to display Dose 5 data.

Figure 23: Dose-Adjusted Exposure by Dose, Groups 1-3, Dose 1

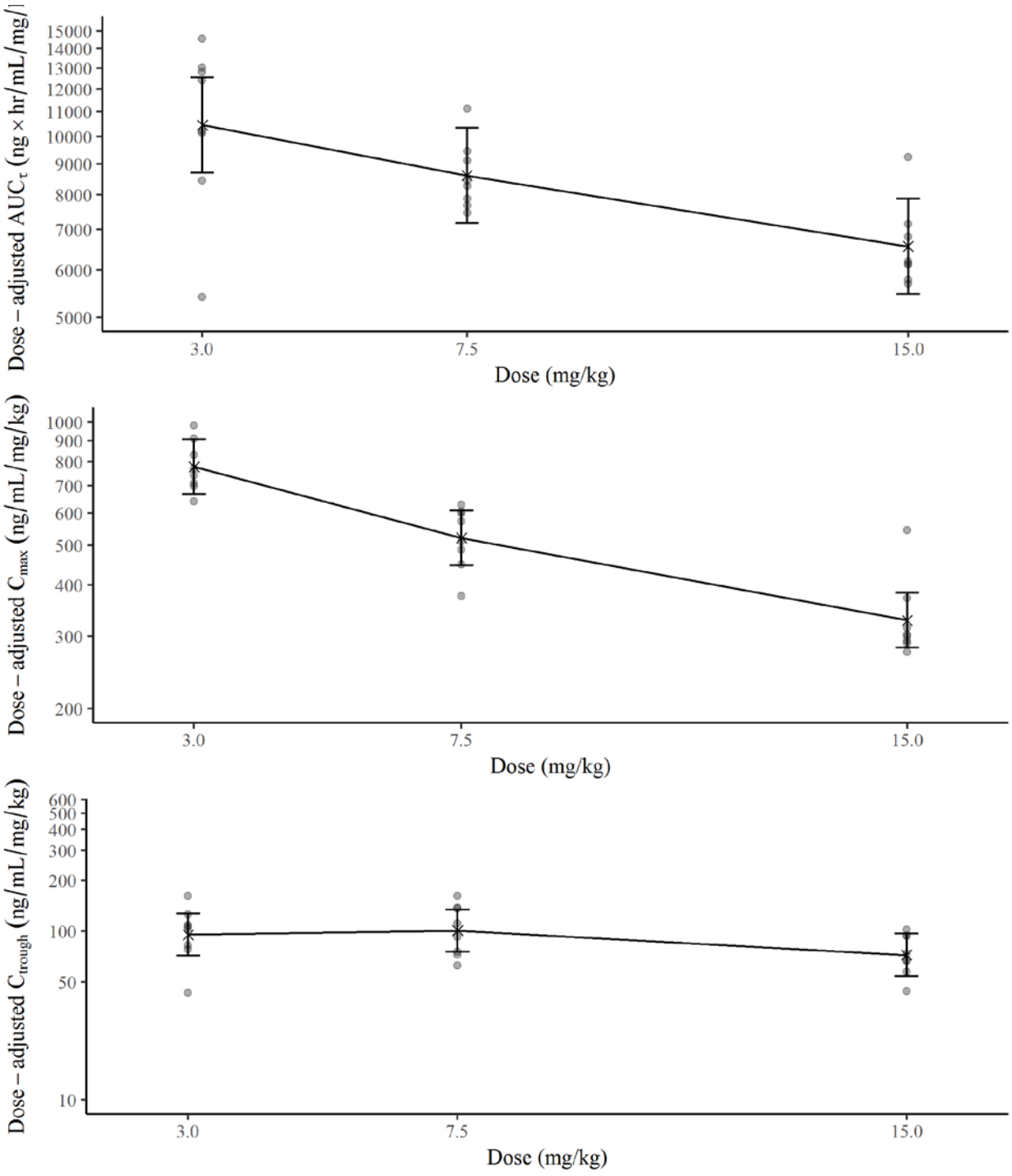
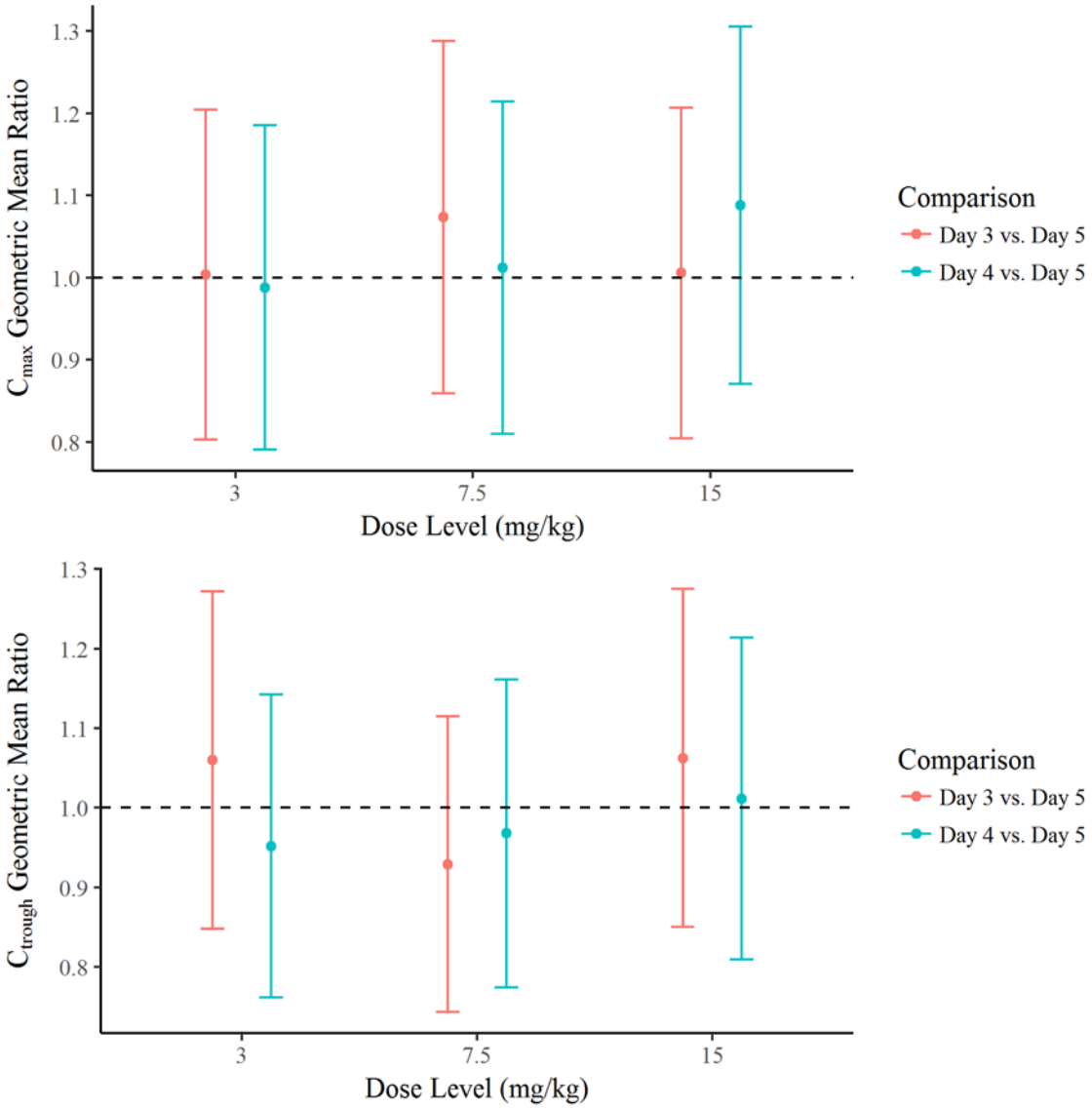


Figure 24: Dose-Adjusted Exposure by Dose, Groups 1-3, Dose 5

This figure will use the form of **Figure 23** to display Dose 5 data.

Figure 25: Assessment of Steady State – Geometric Mean Ratio and 95% CI for C_{max} and C_{trough} on Day 3 and Day 4 Relative to Day 5 by Dose Level



Appendix III: List of Proposed Listings

TABLE OF LISTINGS

Listing 1: Subject Level Demographic and Baseline Characteristics

[Implementation note: Treatment Group will list one of the following, according to Group: "Group 1 (3 mg/kg)," "Group 2 (7.5 mg/kg)," "Group 3 (10 mg/kg)," "Group 4 Sequence A," "Group 4 Sequence B."]

Subject ID	Treatment Group	Sex	Race	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m^2)

Listing 2: Dosing

Subject ID	Treatment Group	Dose (mg)[1]	Dose Number	Nominal Time Since First Dose (day:hour:minute)	Actual Time Since First Dose (day:hour:minute)	Actual Time Since Preceding Dose[2] (day:hour:minute)	Dose Within Time Window
							yes/no

[1] Dose in milligrams calculated as (volume in mL administered) * (concentration of formulation in mg/mL)
[2] Out of window times are indicated by an asterisk

Listing 3: Subject Level Drug Concentrations

Subject ID	Treatment Group	Dose Number	Nominal Time Since First Dose (day:hour: minute)	Actual Time Since First Dose (day:hour: minute)	Actual Time Since Preceding Dose[1] (day:hour: minute)	Drug Concentrations (ng/mL)	Sample Within Time Window	Used in λz Calculations	Excluded from NCA	Reason for Exclusion from NCA
							yes/no	yes/no	yes/no	

[1] Out of window times are indicated by an asterisk

Listing 4: Group 1-3 Subject Level Accumulation Ratios and Shift in T_{max}

Subject ID	Treatment Group	$AR = \frac{AUC_{\tau,Dose\ 5}}{AUC_{\tau,Dose\ 1}}$	$AR = \frac{C_{max,Dose\ 5}}{C_{max,Dose\ 1}}$	$AR = \frac{1}{1 - e^{-\lambda_z \tau}}$	$T_{max,\ Dose\ 5} - T_{max,\ Dose\ 1}$ (hr)

Listing 5: Group 4 Subject Level Exposure Parameters

Subject ID	Sequence	$AUC_{(0-\infty)}$ (ng·hr/mL)			$AUC_{(0-last)}$ (ng·hr/mL)			C_{max} (ng/mL)			T_{max} (hr)		
		Fed	Fasted	Ratio Fed: Fasted	Fed	Fasted	Ratio Fed: Fasted	Fed	Fasted	Ratio Fed: Fasted	Fed	Fasted	Difference Fed- Fasted