A Phase 1, Single-Center, Randomized, 3-Period Crossover Study in Healthy Volunteers to Evaluate the Absorption of WTX101 After Single Dose Administration of an Enteric Coated Formulation with and without food and a Non-Coated Formulation Coadministered with a Proton Pump Inhibitor without Food

Unique Protocol ID:	WTX101-102
NCT Number:	NCT05319912
Date of SAP:	22 May 2014

16.1.9 Documentation of Statistical Methods

16.1.9.1 Pharmacokinetic Analysis

16.1.9.1.1 Pharmacokinetic Analysis Plan

A Phase 1, Single-Center, Randomized, 3-Period Crossover Study in Healthy Volunteers to Evaluate the Absorption of WTX101 After Single Dose Administration of an Enteric Coated Formulation with and without food and a Non-Coated Formulation Coadministered with a Proton Pump Inhibitor without Food

Protocol WTX101-102

Pharmacokinetic Analysis Plan

Version 1
May 22, 2014

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List of Abbreviations

Term	Definition
ANOVA	Analysis of Variance
AUC(0-t)	Area under the plasma concentration-time curve from 0 to the final time with a concentration ≥ LOQ
AUC(inf)	Area under the plasma concentration-time curve from 0 to infinity
BMI	Body Mass Index
CI	Confidence interval
CL/F	Clearance uncorrected for bioavailability
Cmax	Maximum plasma concentration
EC	Enteric coated
F	Bioavailability
GMR	Geometric mean ratio
h	Hour
IM	Intramuscular
kg	Kilogram
LOQ	Validated lower limit of the bioanalytical method
m^2	Squared meter
mg	Milligram
mL	Milliliter
Mo	Molybdenum
MSE	Mean squared error
ng	Nanogram
PK	Pharmacokinetic
PKAP	Pharmacokinetic analysis plan
PPI	Proton pump inhibitor
SAP	Statistical analysis plan
$t_{½}$	Elimination half-life
Tmax	Time of maximum plasma concentration
Vz/F	Volume of distribution uncorrected for bioavailability
WSCV	Within-subject coefficient of variation
λz	Elimination rate constant

1.0 Introduction

This pharmacokinetic analysis plan (PKAP) summarizes the planned presentation and analysis of the clinical pharmacokinetic data from WilsonTherapeutics USA, Inc. Protocol WTX101-102, "A Phase 1, Single-Center, Randomized, 3-Period Crossover Study in Healthy Volunteers to Evaluate the Absorption of WTX101 After Single Dose Administration of an Enteric Coated Formulation with and without food and a Non-Coated Formulation Coadministered with a Proton Pump Inhibitor without Food".

Some of the analyses detailed here may be more detailed or in some aspects slightly different than those described in the protocol. In case of differences, this PKAP would supersede the pharmacokinetic sections in the protocol.

Only the pharmacokinetic analyses are described in this PKAP. The summaries of demographics, baseline characteristics, and safety are detailed in a separate statistical analysis plan (SAP) for this study.

2.0 Study Overview

This is an open-label, 3-treatment, 3-period, 6-sequence, single-dose, randomized crossover study of the pharmacokinetics and comparative bioavailability of WTX101 after administration of an enteric coated (EC) tablet versus an uncoated capsule with a proton pump inhibitor (PPI) and after administration of the EC tablet under fed and fasted conditions.

The treatments to be administered are as follows:

Treatment A: WTX101 EC tablets, 60 mg (2 × 30mg) on Day 1 after an overnight fast.

Treatment B: WTX101 EC tablets, 60 mg (2 × 30mg) on Day 1, 30 minutes after the start of a high calorie / high fat breakfast, preceded by an overnight fast.

Treatment C: Omeprazole 20 mg (1 × 20 mg delayed-release capsule) once-daily (QD) on the mornings of Days -5 to -1 after an overnight fast, omeprazole 20 mg delayed-release capsule at Hour -1 on Day 1 after an overnight fast, and WTX101 uncoated capsules, 60 mg (2 × 30mg) at Hour 0 on Day 1.

Eighteen (18) healthy adult male and female volunteers will be randomly assigned to 1 of 6 treatment sequences, as shown in Table 1.

Table 1: Treatment Sequences.

Sequence	Treatment*		
	Period 1	Period 2	Period 3
1	A	B	C
2	B	C	A
3	C	A	B
4	B	A	C
5	A	C	B
6	C	B	A

*A = WTX101 EC tablets, 60 mg (2 × 30mg) on Day 1 after an overnight fast; B = WTX101 EC tablets, 60 mg (2 × 30mg) on Day 1, 30 minutes after the start of a high calorie / high fat breakfast, preceded by an overnight fast; C = Omeprazole 20 mg (1 × 20 mg delayed-release capsule) once-daily (QD) on the mornings of Days -5 to -1 after an overnight fast, omeprazole 20 mg delayed-release capsule at Hour -1 on Day 1 after an overnight fast, and WTX101 uncoated capsules, 60 mg (2 × 30mg) at Hour 0 on Day 1.

Serial blood samples for the measurement of the plasma concentrations of total molybdenum (Mo) will be obtained over a 192-hour period after each dose. There will be a minimum 14-day washout between the dosing in each period.

3.0 Pharmacokinetic Sampling Schedule

On Study Days 1, 15, and 29 (Periods 1, 2, and 3, respectively), blood samples for the determination of total Mo concentrations will be collected before and at 1, 2, 3, 3.5, 4, 4.5, 5, 6, 7, 7.5, 8, 8.5, 9, 9.5, 10, 12, 14, 16, 24, 36, 48, 72, 96, 120, 144, 168, and 192 hours after dosing. Samples collected through 48 hours will be on an inpatient basis and from 72 through 192 hours on an outpatient basis. There will be a minimum 14-day washout between the dosing in each period.

There will be a total of 84 blood samples for pharmacokinetics per subject, 28 per treatment.

4.0 Blinding and Unblinding

This is an objective study and blinding is not required.

5.0 Interim Analysis

No interim analysis will be conducted.

6.0 Pharmacokinetic Analysis

6.1 Analysis Population

The analysis population will consist of all subjects who complete at least 2 periods of the study and have data sufficient for the determination of PK parameters. Any subjects that are excluded from the analysis will be listed along with the reason for the exclusion.

6.2 Pharmacokinetic Analysis

Actual blood sampling times will be used in all PK analyses. Per protocol times will be used to calculate mean plasma concentrations for tabular and graphical displays. All PK calculations and generation of individual subject plasma concentration vs. time graphs will be done using SAS® for Windows® Version 9.3 or higher under Windows XP Professional or higher. Graphs of mean plasma concentration will be prepared using SigmaPlot for Windows Version 12.5 or higher.

6.2.1 Pharmacokinetic Parameters

Pharmacokinetic parameters for total Mo will be calculated using non-compartmental analysis. Only plasma concentrations equal to or greater than the validated lower limit (LOQ) of the assay will be used in the pharmacokinetic analysis. Plasma concentrations < LOQ will be taken as 0 for the calculation of the descriptive statistics for plasma concentrations at each sampling time. For the PK analysis, plasma concentrations < LOQ that occur from pre-dose to the first concentration ≥ LOQ will be taken as 0 and those that occur thereafter will be taken as missing.

Cmax and Tmax will be taken directly from the data. The elimination rate constant, λz, will be calculated as the negative of the slope of the terminal log-linear segment of the

plasma concentration-time curve. The slope will be determined from a plot of the natural log of the terminal plasma concentrations against time; at least 3 terminal plasma concentration time points, beginning with the final concentration ≥ LOQ, will be selected for the determination of λz and the regression will have a coefficient of determination (r^2) ≥ 0.9000. 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. Elimination half-life (t½) will be calculated according to the following equation:

$$t½ = \frac{0.693}{\lambda z}.$$

Area under the curve to the final sample with a concentration ≥ LOQ [AUC(0-t)] will be calculated using the linear trapezoidal method and extrapolated to infinity [AUC(inf)] using

$$AUC(\text{inf}) = AUC(0-t) + \frac{C_{tf}}{\lambda z}$$

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

Clearance (CL/F) and volume of distribution (Vz/F), uncorrected for bioavailability (F), will be calculated according to

$$CL/F = \frac{Dose}{AUC(\text{inf})} \text{ and } Vz/F = \frac{Dose}{AUC(\text{inf}) \times \lambda z},$$

respectively.

7.0 Statistical Analyses

Individual subject plasma total Mo concentrations, blood sampling times, and PK parameters will be listed by treatment group. Plasma concentrations and PK parameters will be summarized by treatment group using descriptive statistics. Summaries for plasma concentrations will include number, arithmetic mean, standard error, and coefficient of variation, geometric mean and coefficient of variation, and minimum,

median and maximum. Summaries for PK parameters will include number, arithmetic mean, standard deviation, and coefficient of variation, geometric mean and coefficient of variation, and minimum, median, maximum.

7.1 Primary Analysis

The PK parameters for total Mo — Cmax, AUC(0-t), and AUC(inf) —will be compared among treatments using an Analysis of Variance (ANOVA) statistical model with sequence, treatment, and period as the fixed effects and subject within sequence as a random effect, using the natural logarithms of the data.

Confidence intervals (90%) will be constructed for the least squares geometric treatment ratios (GMR) — Treatment B (WTX101 EC Tablet + Food)-to-Treatment A (WTX101 EC Tablet Fasted) and Treatment A (WTX101 EC Tablet Fasted)-to-Treatment C (WTX101 Uncoated Capsule + PPI Fasted) — of all 3 parameters using the natural log-transformed data and the two one-sided t-tests procedure. The GMRs and associated 90% confidence limits (CI) will be exponentiated back to the original scale.

7.2 Secondary Analysis

The within-subject coefficient of variation (WSCV) of Cmax, AUC(0-t), and AUC(inf) will be estimated using

$$WSCV = 100\% \times \sqrt{e^{MSE} - 1}$$

where MSE is the mean squared error from the ANOVA.

7.3 Exploratory Analysis

Relationships between CL/F and Vz/F and body size — weight (kg) and BMI (kg/m² — will be examined graphically for each treatment. If suggested by the graphs, regression models may be fit to the data.

8.0 Quality Control Procedures

All data — random code*, plasma concentrations, dosing and sampling dates and times — will be received electronically, either as SAS datasets or Excel workbooks; no data, at any time, will be entered by hand. The creation of the analysis data sets will be quality controlled by a visual inspection of a graph of each subject's plasma concentration vs. time data to ensure that there are no errors.

The data used to construct summary figures and tables will be created by the SAS programs used to either create the analysis data sets or to perform the pharmacokinetic analyses. Data will be transferred electronically to Excel workbooks, e.g. there will be no data transcription, from which the figures and tables will then be constructed. Figures and tables will be hyperlinked to Appendix listings containing the source data.

As a final check, data from a minimum of two subjects will be selected, analyzed manually in an Excel workbook, and the results verified against those created by the SAS programs.

9.0 Tables, Figures, Appendices

9.1 Tables

Table 1: Summary of total Mo pharmacokinetic parameters after administration of a single 60 mg (2 × 30 mg) dose of WTX101 EC tablets to healthy volunteers under fasted and fed conditions and a single 60 mg (2 × 30 mg) dose of WTX101 uncoated capsules with a PPI under fasted conditions.

Table 2: Statistical analysis of total Mo pharmacokinetic parameters after administration of a single 60 mg (2 × 30 mg) dose of WTX101 EC tablets to healthy volunteers under fasted and fed conditions and a single 60 mg (2 × 30 mg) dose of WTX101 uncoated capsules with a PPI under fasted conditions.

9.2 Figures

Figure 1: Mean plasma concentrations of total Mo administration of a single 60 mg (2 × 30 mg) dose of WTX101 EC tablets to healthy volunteers under fasted and fed conditions — linear axes (left panel) and semi-logarithmic (right panel).

* If not created by Kramer Consulting LLC.

Figure 2: Mean plasma concentrations of total Mo administration of a single 60 mg (2 × 30 mg) dose of WTX101 EC tablets and a single 60 mg (2 × 30 mg) dose of WTX101 uncoated capsules with a PPI to healthy volunteers under fasted conditions conditions — linear axes (left panel) and semi-logarithmic (right panel).

9.3 Appendices

Appendix I: Randomization Code

Appendix II: Individual Subject Plasma Total Mo Concentrations

Appendix III: Individual Subject Blood Sampling Times

Appendix IV: Mean ± Standard Deviation Plasma Total Mo Concentrations (ng/mL)

Appendix V: Individual Subject Total Mo Pharmacokinetic Parameters

Appendix VI: Descriptive Statistics for Total Mo Pharmacokinetic Parameters

Appendix VII: Statistical Analysis of Total Mo Pharmacokinetic Parameters

Appendix VIII: Individual Subject Plasma Total Mo Concentration vs. Time Graphs — Linear Axes

Appendix IX: Individual Subject Plasma Total Mo Concentration vs. Time Graphs — Semi-Logarithmic Axes[†]

[†] Graphs include line segments indicating the range of data used to estimate λz.

16.1.9.1.2 Pharmacokinetic Report

A Phase 1, Single-Center, Randomized, 3-Period Crossover Study in Healthy Volunteers to Evaluate the Absorption of WTX101 After Single Dose Administration of an Enteric Coated Formulation with and without food and a Non-Coated Formulation Coadministered with a Proton Pump Inhibitor without Food

Study WTX101-102

Pharmacokinetic and Statistical Report

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List of Abbreviations

Term	Definition
λz	Elimination rate constant
AUC(0-t)	Area under the plasma concentration-time curve from 0 to the final time with a concentration ≥ LOQ.
AUC(inf)	Area under the plasma concentration-time curve to infinity
BMI	Body Mass Index
CL/F	Total clearance uncorrected for bioavailability (F)
cm	Centimeter
Cmax	Maximum plasma concentration
Cu	Copper
EC	Enteric coated
F	Bioavailability
h	hour
ICP-MS	Inductively coupled plasma mass spectrometry
kg	Kilogram
LOQ	Validated lower limit of the bioanalytical method(s)
m^2	Meter Squares
mg	Milligram
mL	Milliliter
Mo	Molybdenum
MW	Molecular weight
ng	nanogram
PK	Pharmacokinetics
PPI	Proton Pump Inhibitor
QD	Once daily
r^2	Coefficient of determination
t½	Elimination half-life
Tlag	Absorption lag time
Tmax	Time of maximum plasma concentration
UC	Uncoated Capsule
Vz/F	Volume of distribution uncorrected for bioavailability (F)

1.0 Synopsis of Pharmacokinetic Results

Protocol WTX101-102 was an open-label, 3-treatment, 3-period, 6-sequence, single-dose, randomized crossover study of the pharmacokinetics and comparative bioavailability of WTX101 after administration of an Enteric Coated (EC) Tablet versus dosing with the current uncoated capsule (UC) coadministered with a proton pump inhibitor (PPI; omeprazole) under fasting conditions and the effect of dosing an EC Tablet with and without food on the absorption of WTX101. Subjects received, according to a randomization schedule (Appendix I), 1 of the WTX101 treatments. Dosing occurred after an overnight fast (Treatments A and C) or 30 minutes after ingesting a high calorie / high fat meal (Treatment B) and there was a minimum 14-day washout between the dosing in successive periods.

Eighteen (18) subjects were enrolled into and completed the study. One (1) subject had a pre-dose plasma concentration after administration of the EC Tablet Fed that was ≥ LOQ and ≥ 5% of the corresponding Cmax and was excluded from the descriptive statistics and statistical analyses for that treatment. The PK analysis population was therefore comprised of 18 subjects for the EC Tablet Fasted and the UC + PPI Fasted and 17 subjects for the EC Tablet Fed.

- Based on total Mo, administration of the EC Tablet Fasted results in comparable exposure to the UC + PPI Fasted in most subjects.
- Based on total Mo, administration of the EC Tablet Fed results in a 60% to 75% decrease in exposure compared to the EC Tablet Fasted in the majority of subjects.
- The mean t½ for total Mo was essentially the same for all 3 treatments, with an overall mean of ~48 h or 2 days.
- There were no apparent relationships between CL/F and body size (weight, BMI), suggesting that a fixed dose, rather than a dose based on body size, i.e. mg/kg or mg/m², may be appropriate for WTX101.

- The lowest between-subject coefficients of variation (BSCV) for Cmax, AUC(0-t), and AUC(inf) were observed for the UC + PPI Fasted, with an ~2-fold increase when the EC Tablet was administered under fasted conditions and an ~4-fold increase, based on the AUCs, when the EC Tablet was administered under fed conditions.

- Administration of WTX101 either as the UC + PPI or the EC Tablet under fasted conditions should result in comparable plasma concentrations of total Mo in most subjects. However, administration of the EC Tablet under fed conditions results in a large decrease in exposure with increased between-subject variability.

2.0 Introduction

WTX101 is an oral de-coppering agent. It is a bis-choline salt of tetrathiomolybdate, bis[(2-hydroxyethyl)trimethylammonium] tetrathiomolybdate. WTX101 is being developed by Wilson Therapeutics for the treatment of Wilson Disease (WD). WD is a rare autosomal-recessive disorder caused by mutations in the ATP7B gene, resulting in a disturbed copper (Cu) metabolism. In the affected patients, Cu accumulates in the liver and in other tissues including the central nervous system. Left untreated, morbidity is progressive and the condition is eventually fatal.

In previous studies, coadministration of proton pump inhibitors (PPI) has been shown to increase the bioavailability of tetrathiomolybdate and to reduce gastrointestinal side effects. An Enteric Coated (EC) tablet formulation would be expected to offer the same benefits of increased bioavailability and reduced gastrointestinal side effects while avoiding the need to coadminister a PPI.

This study was conducted as a crossover study, aimed at evaluating the absorption of WTX101 from the EC tablet under fed and fasted conditions and compared to the current uncoated capsule (UC) administered with a proton pump inhibitor (PPI; omeprazole) under fasting conditions.

3.0 Objective

The primary objectives of the study were to evaluate:

- The effect of dosing with an EC tablet versus dosing with the current UC coadministered with a PPI under fasting conditions, on the absorption of WTX101.

- The effect of dosing an EC Tablet with and without food on the absorption of WTX101.

- The safety and tolerability of WTX101.

4.0 Study Conduct

4.1 Clinical

This study was conducted at Celerion, 621 Rose Street, Lincoln, NE 68502, under the direction of PPD

A copy of the protocol is included in the clinical summary that accompanies this report.

4.2 Bioanalytical

Plasma concentrations of total molybdenum (Mo) were measured using an Inductively coupled plasma mass spectrometry (ICP-MS) method by QPS Netherlands B.V., Petrus Campersingel 123, 9713 AG Groningen, The Netherlands. A detailed report of the bioanalytical methodology and results accompanies this report.

4.3 Pharmacokinetic and Statistical Analyses

The PK and statistical analyses were done by PPD Kramer Consulting LLC, 14313 Outpost Way, North Potomac, MD 20878, and are the subject of this report.

5.0 Overview of the Study Design

This was an open-label, 3-treatment, 3-period, 6-sequence, single-dose, randomized crossover study of the pharmacokinetics and comparative bioavailability of WTX101 after administration of an EC Tablet versus dosing with the current UC + PPI under fasting conditions and the effect of dosing an EC Tablet with and without food on the absorption of WTX101.

The treatments to be administered were as follows:

Treatment A: WTX101 EC Tablets, 60 mg (2 × 30 mg) at Hour 0 on Day 1 following an overnight fast.

Treatment B: WTX101 EC Tablets, 60 mg (2 × 30 mg) at Hour 0 on Day 1, 30 minutes after the start of a high-fat breakfast, preceded by an overnight fast.

Treatment C: WTX101 UC, 60 mg (2 × 30 mg), after an overnight fast, preceded by omeprazole 20 mg (1 × 20 mg delayed-release tablet) once-daily the mornings of Day -5 to Day -1.

Eighteen (18) healthy adult male and female volunteers were randomly assigned (Appendix I) to 1 of 6 treatment sequences, as shown in Table 1.

Table 1: Treatment Sequences.

Sequence	Treatment*		
	Period 1	Period 2	Period 3
1	A	B	C
2	B	C	A
3	C	A	B
4	B	A	C
5	A	C	B
6	C	B	A

*A = WTX101 EC Tablets, 60 mg (2 × 30 mg) fasted; B = WTX101 EC Tablets, 60 mg (2 × 30 mg) fed; C = WTX101 UC 60 mg (2 × 30 mg) + PPI fasted

On Study Days 1, 15, and 29 (Periods 1, 2, and 3, respectively), blood samples for the determination of total Mo concentrations were collected before and at 1, 2, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168, and 192 hours after dosing. Samples collected through 48 hours were on an inpatient basis and from 72 through 192 hours on an outpatient basis. There was a minimum 14-day washout between the dosing in each period.

6.0 Pharmacokinetic and Statistical Methods

6.1 Pharmacokinetic Methods

All PK parameters were calculated using non-compartmental analysis. Only those plasma concentrations equal to or greater than the respective LOQ (total Mo –

0.1 ng/mL) were used in the analysis. Plasma concentrations < LOQ were taken as 0 for the calculation of the descriptive statistics for plasma concentrations at each sampling time. For the pharmacokinetic analysis, plasma concentrations < LOQ that occurred from pre-dose to the first concentration ≥ LOQ were treated as 0 and those that occur thereafter were treated as missing. Actual sampling times were used for all pharmacokinetic analyses. Protocol times were used to calculate mean plasma concentrations for graphical displays.

The maximum plasma concentration (Cmax) and time to Cmax (Tmax) were taken directly from the data. If the plasma concentration at the 1st sample after drug administration — 1 h — was < LOQ, then the absorption lag time (Tlag) was taken as the 1st succeeding sampling time with a concentration ≥ LOQ. The elimination rate constant, λz, was calculated as the negative of the slope of the terminal log-linear segment of the plasma concentration-time curve. The slope was determined from a plot of the natural log of the terminal plasma concentrations against time; at least 3 terminal plasma concentration time points, beginning with the final concentration ≥ LOQ, were selected for the determination of λz and the regression will have a coefficient of determination (r^2) ≥ 0.9000. The range of data used for each subject and treatment was determined by visual inspection of a semi-logarithmic plot of concentration vs. time. Elimination half-life (t½) was calculated according to the following equation.

$$t½ = \frac{0.693}{\lambda z}$$

Area under the curve from zero to the final sample with a concentration ≥ LOQ [AUC(0-t)] was calculated using the linear trapezoidal method and extrapolated to infinity [AUC(inf)] using

$$AUC(\text{inf}) = AUC(0-t) + \frac{C_{tf}}{\lambda z}$$

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

The clearance (CL/F) and volume of distribution (Vz/F) of Mo, uncorrected for bioavailability (F), were calculated according to

$$CL/F = \frac{Dose}{AUC(\text{inf})} \text{ and } Vz/F = \frac{Dose}{AUC(\text{inf}) \times \lambda z},$$

respectively, where Dose represents the dose of Mo. The molecular weights (MW) of WTX101 and Mo are 432.52 and 95.94, respectively, and thus 60 mg of WTX101 represents 13.3 mg of Mo.

All pharmacokinetic calculations were done and individual subject plasma concentration-time graphs were prepared using SAS® for Windows® Version 9.3. Graphs of mean plasma concentration vs. time and other in-text graphs were prepared using SigmaPlot for Windows Version 12.5.

6.2 Statistical Methods

Plasma concentrations, actual blood sampling times, and pharmacokinetic parameters are listed; concentrations and pharmacokinetic parameters are summarized using descriptive statistics.

All statistical analyses were done using SAS® for Windows® Version 9.3.

6.2.1 Primary Analysis

The PK parameters for total Mo — Cmax, AUC(0-t), and AUC(inf) — were compared between treatments using an Analysis of Variance (ANOVA) statistical model with sequence, treatment, and period as the fixed effects and subject within sequence as a random effect, using the natural logarithms of the data.

Confidence intervals (90%) were constructed for the least squares geometric mean ratios (GMR) — Treatment B (EC Tablet Fed)-to-Treatment A (EC Tablet Fasted) and Treatment A (EC tablet Fasted)-to-Treatment C (UC + PPI Fasted) — of all 3 parameters using the natural log-transformed data and the two one-sided t-tests procedure. The GMRs and associated 90% confidence limits (CI) were exponentiated back to the original scale.

6.2.2 Secondary Analysis

The within-subject coefficient of variation (WSCV) of Cmax, AUC(0-t), and AUC(inf) were estimated using

$$WSCV = 100\% \times \sqrt{e^{MSE} - 1}$$

where MSE is the mean squared error from the ANOVA.

6.2.3 Exploratory Analysis

Relationships between CL/F and body size — weight (kg) and BMI (kg/m² — were examined graphically for each treatment. If suggested by the graphs, regression models could be fit to the data.

7.0 Results

The random code is shown in Appendix I and the individual subject body size — weight and body mass index (BMI) — are listed in Appendix II. The individual subject plasma total Mo concentrations, actual blood sampling times, and descriptive statistics for plasma concentrations are listed in Appendix III, Appendix IV, and Appendix V respectively. Individual subject PK parameters are listed in Appendix VI and the associated descriptive statistics for the PK parameters are in Appendix VII. The statistical analysis of the total Mo PK parameters is in Appendix VIII. Individual subject graphs of plasma total Mo concentration vs. time on linear axes can be found in Appendix IX and on semi-logarithmic axes in Appendix X. The latter contains line segments indicating the range of data used to estimate λz for those datasets for which it could be estimated.

7.1 Subjects with a Pre-Dose Concentration ≥ LOQ

Two (2) subjects had a plasma total Mo concentration prior to dosing in Period 2 that was ≥ LOQ (0.1 ng/mL) (Table 2). For Subject PPD the pre-dose concentration was 40.60% of the corresponding Cmax and the data for this treatment — EC Tablet Fed — for this subject was excluded from the descriptive statistics and statistical analyses.[1] For Subject PPD the pre-dose concentration after administration of the UC + PPI Fasted was < 5% of

the corresponding Cmax (Table 2) and the data were therefore included in the descriptive statistics and the PK and statistical analyses.[1]

Table 2: Subjects with a pre-dose concentration ≥ LOQ.

Subject	Period	Treatment	C(0) (ng/mL)	Cmax (ng/mL)	Ratio* (%)
PPD	2	EC Tablet Fed	12.34	30.39	40.60
	2	UC + PPI Fasted	10.28	375.17	2.74

*Ratios ≥ 5% are shown in red.

Source: C(0) – Appendix III; Cmax – Appendix VI.

7.2 Pharmacokinetic Analysis Population

Eighteen (18) subjects were enrolled into and all completed the study. As discussed in Section 7.1, the data for Subject PPD for the EC Tablet Fed were excluded from the descriptive statistics and statistical analyses. The PK analysis population was therefore comprised of 18 subjects for the EC Tablet Fasted and the UC + PPI Fasted and 17 subjects for the EC Tablet Fed.

7.3 Pharmacokinetics

7.3.1 Results

The mean ± standard error plasma concentrations of total Mo are shown in.

As shown in Figure 1, the mean ± standard error plasma concentrations of total Mo were slightly lower after administration of the EC Tablet Fasted compared to the UC + PPI Fasted. There was, however, variability among subjects with 3 of the 18 showing much lower concentrations for the EC Tablet, 5 showing the same pattern as the mean data, and 10 showing more comparable or superimposable concentrations for both treatments (Appendix IX).

Consistent with the mean plasma concentrations, the arithmetic (Table 3) and geometric (Table 4) mean values for Cmax, AUC(0-t), and AUC(inf) were lower for the EC Tablet Fasted than for the UC Capsule + PPI Fasted. The GMRs ranged from 75.81% to 87.16% with lower limits of the associated 90% CIs < 80.00% (Table 4), indicating a decrease in exposure *on the average*. The median Tmax was comparable for both

treatments, 4.54 h and 4.50 h, respectively, with comparable ranges (Table 3). Four (4) of the 18 subjects had an absorption lag time after administration of the EC Tablet fasted with a median (range) of 2.00 h (2.00 h to 3.00 h) (Table 3).

Administration of the EC Tablet with food resulted in a large decrease in the mean plasma total Mo concentrations (Figure 1). This was also observed in all but 2 of the 17 subjects evaluable for this treatment (Appendix IX). Cmax, AUC(0-t), and AUC(inf) were lower after administration of the EC Tablet with food (Table 3, Table 4) with GMRs ranging from 25.20% to 40.49%, indicating a substantial decrease in absorption. The median Tmax was comparable with and without food, 4.55 h and 4.54 h, respectively, with comparable ranges (Table 3). Compared to the EC Tablet Fasted, more subjects (6) had an absorption lag time an increase in the median (range) to 3.00 h (2.00 h to 5.00 h) (Table 3).

The mean t½ was essentially the same for all 3 treatments (Table 3), with an overall mean of ~48 h or 2 days.

The relationships between Mo CL/F and body size, expressed as weight and BMI, are illustrated in Figure 2 (Treatment A — EC Tablet Fasted) and Figure 3 (Treatment C — UC + PPI Fasted).[1] There are no apparent relationships between CL/F and either measure of body size. This suggests that a fixed dose, rather than a dose based on body size, i.e. mg/kg or mg/m², may be appropriate for WTX101.

The lowest between-subject coefficients of variation (BSCV) for Cmax, AUC(0-t), and AUC(inf) were observed for the UC capsule + PPI Fasted, with values ranging from 15.8% to 19.1% (Table 5). Administration of the EC Tablet Fasted resulted in higher BSCVs (26.1% to 35.2%; Table 5). The BSCVs were much higher, particularly for AUC(0-t) and AUC(inf) — 81.5% and 72.6%, respectively (Table 5) — when the EC Tablet was administered after the high calorie / high fat meal. Compared to the EC

[1] Due to the slight but apparent differences in bioavailability among the treatments, the relationships between CL/F and body size are shown separately for the 2 fasted treatments. As a consequence of the low bioavailability after administration of the EC Tablet Fed, it was excluded from this analysis.

Tablet Fasted, the BSCVs for the AUCs were ~2.2-fold higher when the EC Tablet was administered under fed conditions.

Figure 1: Mean ± standard error plasma concentrations of total Mo after administration of a single 60 mg (2 × 30 mg) dose of WTX101 EC Tablets under fasted and fed conditions and UC + PPI under fasted conditions — linear axes (left panel) and semi-logarithmic (right panel).

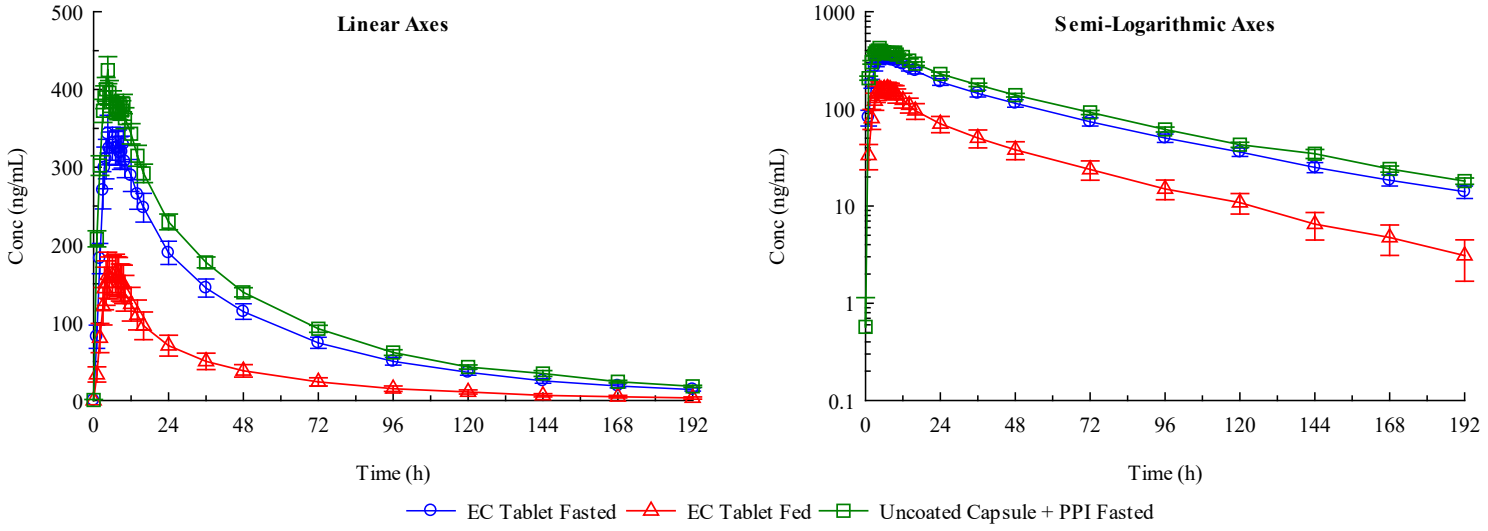


Table 3: Summary of total Mo PK parameters after administration of a single 60 mg (2 × 30 mg) dose of WTX101 EC Tablets under fasted and fed conditions and UC + PPI under fasted conditions.

Parameter*	Treatment		
	EC Tablet Fasted	EC Tablet Fed	UC + PPI Fasted
Tlag (h)	2.00 (4) [2.00 – 3.00]	3.00 (6) [2.00 – 5.00]	—†
Cmax (ng/mL)	376 ± 98.0 (18)	187 ± 118 (17)	442 ± 69.6 (18)
Tmax (h)	4.54 (18) [3.00 – 9.53]	4.55 (17) [3.52 – 9.51]	4.50 (18) [2.99 – 10.0]
AUC(0-t) (h×ng/mL)	16,026 ± 5,635 (18)	5,740 ± 4,681 (17)	19,809 ± 3,509 (18)
AUC(inf) (h×ng/mL)	17,258 ± 5,955 (18)	6,973 ± 5,065 (15)	21,047 ± 4,022 (17)
λz (1/h)	0.0140 ± 0.0023 (18)	0.0258 ± 0.0303 (15)	0.0145 ± 0.0014 (17)
t½ (h)	51.0 ± 8.87 (18)	43.5 ± 20.9 (15)	48.2 ± 4.86 (17)
CL/F (L/h)	0.92 ± 0.51 (18)	6.34 ± 11.9 (15)	0.66 ± 0.13 (17)
Vz/F (L)	66.6 ± 34.0 (18)	175 ± 98.1 (15)	45.2 ± 8.31 (17)

*Arithmetic mean ± standard deviation (N) except for Tmax for which the median (N) [Range] is reported. Additional descriptive statistics can be found in Appendix VII.
†Parameter could not be estimated for any subject for this treatment.

Source: Appendix VII.

Table 4: Statistical analysis of total Mo PK parameters after administration of a single 60 mg (2 × 30 mg) dose of WTX101 EC Tablets under fasted and fed conditions and UC + PPI under fasted conditions.

Parameter	Least Squares Geometric Means		Geometric Mean Ratio (%)*				Within-Subject CV (%)
	Test	Reference	Estimate	90% Confidence Interval			
EC Tablet Fasted vs. UC + PPI Fasted							
Cmax	360.88	436.61	82.65	63.91	→	106.90	47.98
AUC(0-t)	14,790.84	19,511.14	75.81	52.23	→	110.02	73.76
AUC(inf)	15,997.76	18,353.45	87.16	64.59	→	117.63	55.30
EC Tablet Fed vs. EC Tablet Fasted							
Cmax	146.11	360.88	40.49	31.12	→	52.68	47.98
AUC(0-t)	3,726.71	14,790.84	25.20	17.21	→	36.89	73.76
AUC(inf)	5,071.14	15,997.76	31.70	23.12	→	43.47	55.30

*Based on analysis of natural log-transformed data.

Source: Appendix VIII.

Figure 2: Individual subject CL/F vs. body weight (left panel) and BMI (right panel) of total Mo after administration of a single 60 mg (2 × 30 mg) dose of WTX101 EC Tablets fasted to healthy volunteers.

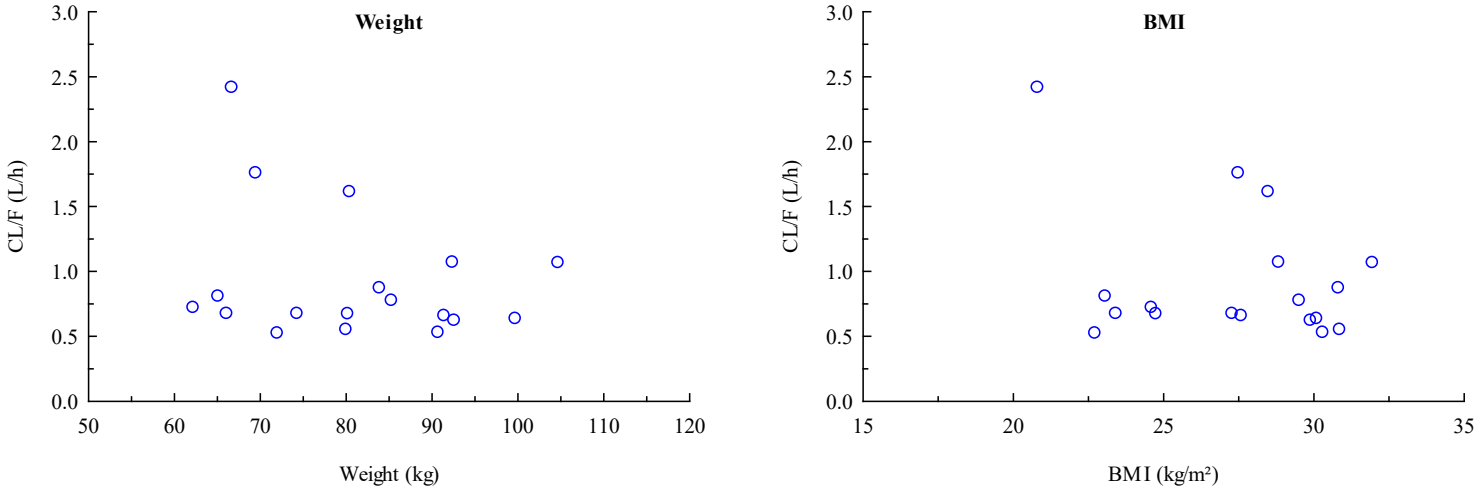


Figure 3: Individual subject CL/F vs. body weight (left panel) and BMI (right panel) of total Mo after administration of a single 60 mg (2 × 30 mg) dose of WTX101 uncoated capsules + PPI fasted to healthy volunteers.

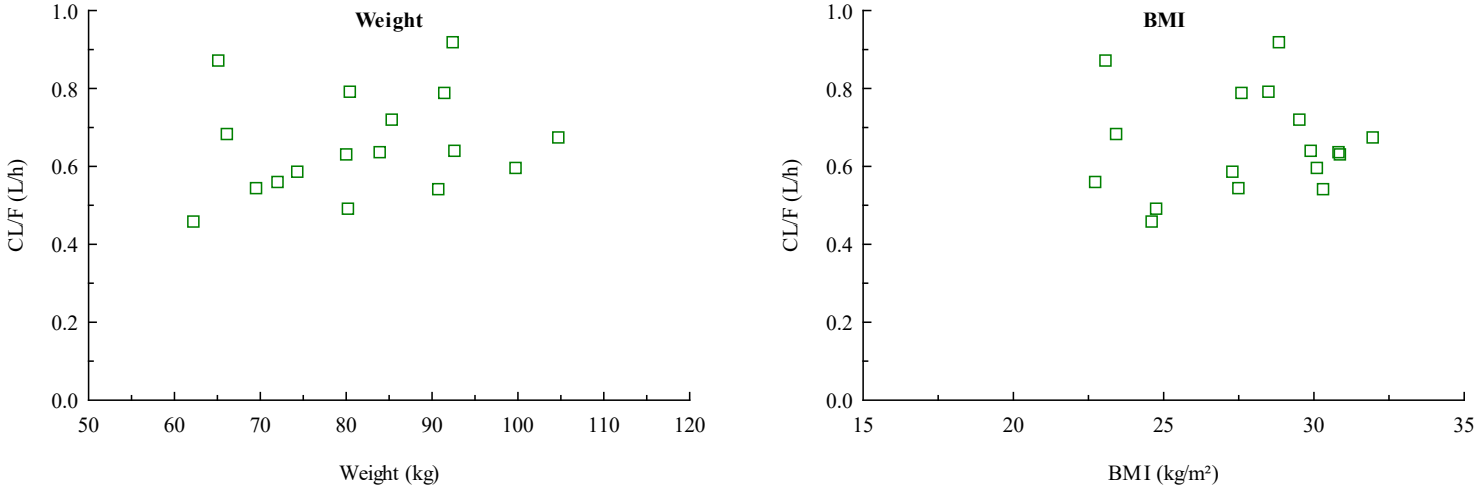


Table 5: Summary of between-subject coefficients of variation of total Mo Cmax, AUC(0-t), and AUC(inf) after administration of a single 60 mg (2 × 30 mg) dose of WTX101 EC Tablets under fasted and fed conditions and UC + PPI under fasted conditions.

Parameter*	Treatment		
	EC Tablet Fasted	EC Tablet Fed	UC + PPI Fasted
Cmax (ng/mL)	26.1	39.9	15.8
AUC(0-t) (h×ng/mL)	35.2	81.5	17.7
AUC(inf) (h×ng/mL)	34.5	72.6	19.1

*Between-subject coefficient of variation (%).

Source: Appendix VII.

7.3.2 Discussion

As illustrated in Figure 1, there was a slight decrease in the mean ± standard error plasma concentrations of total Mo after administration of the EC Tablet Fasted compared to the UC + PPI fasted. Similar trends were observed with respect to Cmax, AUC(0-t), and AUC(inf) (Table 3 and Table 4). Nevertheless, examination of the individual subject data (PK parameters — Appendix VI; graphs of plasma concentrations — Appendix IX) indicates that while a similar pattern was observed with some of the individual subjects, the majority had a total Mo concentration-time profile that was comparable for the EC Tablet and UC + PPI when both were administered under fasted conditions. However, administration of the EC Tablet fed resulted in a 60% to 75% decrease in absorption which was consistent among the majority of subjects (Appendix IX).

Administration of WTX101 as the EC Tablet increased the between-subject variability compared to the UC + PPI, ~2-fold when administered under fasted conditions and ~4-fold, based on the AUCs, when administered under fed conditions.

8.0 Conclusions

- Based on total Mo, administration of the EC Tablet Fasted results in comparable exposure to the UC + PPI Fasted in most subjects.
- Based on total Mo, administration of the EC Tablet Fed results in a 60% to 75% decrease in exposure compared to the EC Tablet Fasted in the majority of subjects.
- The mean t½ for total Mo was essentially the same for all 3 treatments, with an overall mean of ~48 h or 2 days.
- There were no apparent relationships between CL/F and body size (weight, BMI), suggesting that a fixed dose, rather than a dose based on body size, i.e. mg/kg or mg/m², may be appropriate for WTX101.
- The lowest between-subject coefficients of variation (BSCV) for Cmax, AUC(0-t), and AUC(inf) were observed for the UC + PPI Fasted, with an ~2-fold increase when

the EC Tablet was administered under fasted conditions and an ~4-fold increase, based on the AUCs, when the EC Tablet was administered under fed conditions.

- Administration of WTX101 either as the UC + PPI or the EC Tablet under fasted conditions should result in comparable plasma concentrations of total Mo in most subjects. However, administration of the EC Tablet under fed conditions results in a large decrease in exposure with increased between-subject variability.

9.0 References

1. Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), March, 2003.

Appendix I
Random Code

Subject	Sequence	Treatment Period 1	Treatment Period 2	Treatment Period 3
PPD	BCA	B	C	A
	BAC	B	A	C
	ABC	A	B	C
	CAB	C	A	B
	ACB	A	C	B
	CBA	C	B	A
	BCA	B	C	A
	ABC	A	B	C
	CBA	C	B	A
	CAB	C	A	B
	ACB	A	C	B
	BAC	B	A	C
	BAC	B	A	C
	CBA	C	B	A
	ABC	A	B	C
	BCA	B	C	A
	CAB	C	A	B
	ACB	A	C	B

Treatment A - EC Tablet Fasted; Treatment B - EC Tablet Fed; Treatment C - Uncoated Capsule + PPI Fasted

Appendix II
Subject Sex, Height, Weight, and BMI

Subject	Sex	Height (cm)*	Weight (kg)*	BMI (kg/m²)§
PPD		179	66.7	20.82
		179	92.4	28.84
		168	80.4	28.49
		170	85.3	29.52
		180	80.2	24.75
		173	90.7	30.31
		161	80.0	30.86
		182	91.4	27.59
		165	74.3	27.29
		159	62.2	24.60
		176	92.6	29.89
		168	66.1	23.42
		182	99.7	30.10
		165	83.9	30.82
		181	104.7	31.96
		159	69.5	27.49
		168	65.1	23.07
		178	72.0	22.72

*Screening values.
§Calculated from height and weight.

Appendix III
Individual Subject Plasma Concentrations
Treatment A - EC Tablet Fasted

Subject	Period	Scheduled Time (h) 0	1	2	3	3.5	4	4.5	5	6	7	7.5	8	8.5	9
PPD	3	0.00	98.18	125.71	138.32	134.78	134.68	147.29	144.71	127.97	115.04	116.83	112.36	117.64	105.05
	2	0.00	131.56	181.29	254.30	259.03	265.79	259.69	236.91	232.83	236.22	249.49	258.13	269.11	261.36
	1	0.00	103.85	123.14	201.11	228.55	235.67	278.51	254.12	233.12	222.06	218.52	208.76	211.79	210.42
	2	0.00	216.94	291.58	441.89	426.36	384.91	386.73	359.17	343.18	348.62	329.94	328.22	314.16	314.27
	1	0.00	0.00	0.00	137.20	178.68	193.81	264.12	256.91	361.37	391.14	397.87	390.01	349.42	366.02
	3	0.00	51.16	230.61	322.23	381.35	396.83	450.27	407.18	395.63	430.82	417.64	441.73	420.96	416.72
	3	0.00	34.22	218.85	366.40	401.36	399.91	445.21	434.97	459.26	466.89	471.67	460.54	443.90	406.51
	1	0.00	103.97	215.77	372.46	411.20	361.31	393.54	339.88	335.44	342.55	335.99	340.47	338.79	350.50
	3	0.00	0.00	176.32	250.96	285.75	323.16	378.18	421.52	450.94	422.34	419.15	410.65	384.26	396.16
	2	0.00	126.94	224.27	325.68	389.12	407.87	424.72	377.99	345.06	340.38	350.33	350.58	347.63	346.22
	1	0.00	85.14	207.71	291.54	329.85	325.93	362.73	359.79	333.19	350.12	342.13	345.30	346.02	363.13
	2	0.00	47.05	284.76	348.80	429.67	445.57	445.60	392.73	363.19	352.16	346.38	364.62	361.13	345.61
	2	0.00	131.22	232.84	309.63	288.91	283.82	337.12	313.26	295.05	268.31	272.14	301.30	293.73	328.17
	3	0.00	164.45	281.99	344.07	366.83	392.60	349.50	317.17	313.08	295.65	312.10	314.15	288.54	308.53
	1	0.00	41.02	58.40	56.51	62.06	121.48	185.29	226.50	355.54	296.63	297.73	296.64	277.83	292.64
	3	0.00	0.00	51.89	143.01	145.26	166.39	213.74	212.31	218.93	217.18	219.93	198.39	207.42	205.77
	2	0.00	137.79	182.76	224.62	252.50	271.86	312.57	298.54	298.64	289.98	286.18	279.42	273.04	268.70
	1	0.00	0.00	195.53	337.83	413.32	478.14	533.87	483.43	483.92	461.07	460.39	464.76	484.69	467.48

Assay LOQ = 10 ng/mL
(. = no sample analyzed and/or reported)

Appendix III
Individual Subject Plasma Concentrations
Treatment A - EC Tablet Fasted

		Scheduled Time (h)													
Subject	Period	9.5	10	12	14	16	24	36	48	72	96	120	144	168	192
PPD	3	112.76	99.92	95.51	88.90	79.60	60.92	47.59	35.30	21.94	14.71	10.78	0.00	0.00	0.00
	2	260.79	236.14	227.19	204.69	185.09	147.11	107.47	82.48	50.55	33.55	22.31	16.23	12.86	0.00
	1	225.06	205.92	176.43	157.93	152.88	97.47	69.32	51.19	30.31	17.98	12.76	0.00	0.00	0.00
	2	304.71	319.67	285.85	255.60	259.52	192.44	142.28	110.57	67.51	44.77	32.70	23.54	16.08	14.88
	1	352.32	348.76	335.61	316.58	294.79	225.15	173.69	129.75	93.38	63.95	47.64	32.45	22.88	17.83
	3	430.28	386.82	365.13	309.13	300.81	241.06	184.14	153.41	115.16	82.92	65.42	48.90	36.43	29.78
	3	483.93	439.16	412.80	380.54	356.82	278.09	197.75	165.38	109.70	71.94	48.97	35.21	26.33	21.32
	1	355.05	318.66	307.43	284.51	268.49	217.31	179.06	143.01	103.58	64.34	43.22	32.54	21.89	15.20
	3	402.79	381.36	343.25	336.71	312.59	229.49	170.57	139.00	83.68	56.87	38.65	25.64	19.56	14.94
	2	336.90	322.15	306.96	257.42	249.45	195.73	142.86	104.51	66.33	49.72	37.37	30.10	23.43	19.41
	1	382.79	339.11	336.56	305.76	284.98	218.45	176.12	142.62	94.04	69.13	48.73	36.28	27.56	23.57
	2	359.32	337.47	337.98	301.69	289.11	214.49	175.84	142.55	85.27	59.90	37.70	28.21	20.62	15.45
	2	370.37	353.17	322.89	323.13	300.35	232.70	184.84	148.69	95.31	63.80	47.80	32.00	26.70	19.35
	3	293.83	282.71	253.88	236.86	215.28	171.24	128.20	93.85	54.15	38.16	27.71	18.25	16.10	13.73
	1	283.95	262.86	235.97	217.67	179.96	139.98	108.75	80.09	49.45	31.58	24.04	17.77	14.03	10.97
	3	210.84	187.51	161.23	143.24	127.83	88.49	59.00	40.87	24.61	16.68	13.42	10.12	0.00	0.00
	2	288.20	266.03	263.01	249.57	231.03	170.63	135.96	115.92	72.60	47.06	37.47	27.27	21.64	15.26
	1	471.19	445.84	441.49	397.88	371.79	294.46	217.24	177.90	115.12	78.30	52.94	37.19	27.53	21.02

Assay LOQ = 10 ng/mL
(. = no sample analyzed and/or reported)

Appendix III
Individual Subject Plasma Concentrations
Treatment B - EC Tablet Fed

Subject	Period	Scheduled Time (h) 0	1	2	3	3.5	4	4.5	5	6	7	7.5	8	8.5	9
PPD	1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	12.85	21.31	26.61	27.15	26.70	24.40	23.84
	1	0.00	0.00	19.53	73.01	103.86	122.75	144.33	144.19	136.16	125.60	124.38	118.22	112.11	109.29
	2	0.00	0.00	0.00	55.41	64.64	62.62	71.48	63.85	63.03	63.23	64.01	60.00	63.17	59.68
	3	0.00	17.63	163.84	295.07	338.70	365.88	386.35	369.95	362.28	355.71	357.16	362.04	351.14	361.03
	3	0.00	18.50	31.04	40.99	50.52	55.02	64.10	64.88	69.05	75.27	73.47	69.96	67.68	64.73
	2	12.34	11.91	11.82	16.32	18.79	20.68	24.66	26.31	27.81	29.98	30.06	30.39	29.06	29.90
	1	0.00	10.56	10.90	14.69	17.40	21.24	29.16	33.80	41.03	45.72	45.31	44.84	44.00	42.00
	2	0.00	100.70	223.00	270.10	278.69	250.68	246.98	224.48	203.37	186.22	177.73	170.61	172.76	163.03
	2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	41.25	152.93	264.01	313.69	315.30	303.47	293.78
	3	0.00	0.00	69.44	155.16	180.68	214.36	231.05	226.73	247.67	250.60	228.21	235.55	231.30	213.13
	3	0.00	12.76	60.13	65.00	68.49	68.42	72.27	69.50	73.25	67.49	68.82	65.18	61.54	61.15
	1	0.00	0.00	0.00	95.61	269.48	294.17	314.87	298.13	290.46	298.33	265.11	265.05	236.01	264.11
	1	0.00	93.68	185.96	206.87	224.37	240.28	256.51	249.79	234.39	215.20	196.05	200.88	183.31	187.43
	2	0.00	122.88	116.09	123.52	127.48	125.11	137.05	130.62	120.55	120.76	114.42	121.14	112.86	118.34
	2	0.00	43.93	71.15	74.60	81.63	79.24	87.43	81.91	75.72	72.43	69.18	65.51	66.65	64.04
	1	0.00	63.64	174.22	232.66	264.35	262.92	272.07	264.48	257.48	228.43	234.69	218.01	208.02	202.39
	3	0.00	34.52	62.27	81.62	84.74	93.57	99.11	101.54	100.88	108.85	106.91	102.02	95.32	96.57
	3	0.00	48.89	176.75	273.72	293.40	309.80	325.45	298.39	290.22	270.46	254.53	258.93	244.79	238.98

Assay LOQ = 10 ng/mL
(. = no sample analyzed and/or reported)

Appendix III
Individual Subject Plasma Concentrations
Treatment B - EC Tablet Fed

		Scheduled Time (h)													
Subject	Period	9.5	10	12	14	16	24	36	48	72	96	120	144	168	192
PPD	1	22.74	20.35	15.83	12.49	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	1	102.40	93.88	83.54	70.40	58.36	41.73	28.68	20.40	12.26	0.00	0.00	0.00	0.00	0.00
	2	61.95	54.64	44.48	40.03	36.43	27.97	14.59	11.88	0.00	0.00	0.00	0.00	0.00	0.00
	3	387.75	361.80	336.48	287.92	271.27	205.55	164.40	123.25	81.51	46.99	31.11	22.42	16.87	14.10
	3	62.74	58.63	44.76	36.19	31.43	19.73	13.19	12.01	11.41	0.00	0.00	0.00	0.00	0.00
	2	29.11	29.40	27.63	25.66	23.05	20.66	17.83	16.93	14.94	13.13	12.08	10.85	10.26	0.00
	1	40.88	38.50	31.95	25.93	22.45	15.08	10.09	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	2	144.14	150.50	129.38	116.44	104.83	77.62	56.59	44.71	33.05	20.90	16.58	12.05	11.52	0.00
	2	282.58	266.41	253.46	220.59	198.89	148.90	111.04	87.57	53.12	32.67	27.06	20.49	14.68	14.61
	3	209.67	197.77	166.45	161.87	135.22	99.25	73.16	49.52	34.18	27.16	20.07	14.23	12.49	11.45
	3	59.32	54.39	51.61	47.20	40.48	33.12	22.31	19.44	14.26	11.45	11.03	0.00	0.00	0.00
	1	243.44	217.27	206.65	202.29	168.90	124.03	88.83	70.95	40.85	26.10	19.04	12.84	10.08	0.00
	1	184.59	164.35	151.38	133.58	114.28	81.36	60.24	45.75	27.43	20.26	14.02	10.87	0.00	0.00
	2	119.70	112.78	104.55	95.49	83.22	59.42	36.81	28.19	17.43	12.95	0.00	0.00	0.00	0.00
	2	63.03	53.90	47.35	42.35	38.05	24.95	15.97	13.13	0.00	0.00	0.00	0.00	0.00	0.00
	1	214.18	193.12	165.25	148.12	122.52	86.84	53.00	39.10	22.72	16.69	12.37	0.00	0.00	0.00
	3	95.97	87.71	70.99	58.05	48.75	33.42	22.46	20.53	15.56	11.45	10.51	0.00	0.00	0.00
	3	241.80	217.08	199.77	170.73	155.83	118.87	82.46	60.69	42.21	29.73	22.87	17.90	15.04	12.28

Assay LOQ = 10 ng/mL
(. = no sample analyzed and/or reported)

Appendix III
Individual Subject Plasma Concentrations
Treatment C - Uncoated Capsule + PPI Fasted

		Scheduled Time (h)													
Subject	Period	0	1	2	3	3.5	4	4.5	5	6	7	7.5	8	8.5	9
PPD	2	0.00	224.42	321.57	445.77	415.87	396.83	438.76	395.75	384.80	374.79	372.45	347.23	374.22	356.89
	3	0.00	192.87	226.09	306.50	353.87	320.33	313.55	293.74	303.75	302.48	291.78	296.67	303.73	303.22
	3	0.00	191.87	283.68	347.63	351.11	377.14	447.08	416.43	397.65	383.91	363.62	352.14	366.16	347.99
	1	0.00	177.57	327.32	409.25	399.03	418.87	460.34	386.95	375.68	381.60	356.53	374.77	378.81	367.19
	2	0.00	292.36	344.86	361.71	347.34	349.25	366.44	390.67	392.11	375.63	393.39	403.71	398.74	402.12
	1	0.00	146.44	297.86	371.24	367.63	392.13	402.97	375.76	394.88	376.46	383.51	388.41	393.68	381.60
	2	0.00	187.04	278.25	391.55	411.06	417.43	459.34	433.49	416.44	417.04	410.70	400.32	402.69	403.65
	3	0.00	172.51	302.15	346.64	366.56	359.30	367.72	327.67	327.51	320.73	303.08	300.30	304.80	299.41
	1	0.00	284.76	414.18	444.73	477.57	439.41	445.33	408.90	406.91	398.53	388.18	385.06	381.33	386.98
	1	0.00	217.16	347.86	421.06	422.30	504.29	566.16	508.98	494.04	484.56	453.48	454.36	462.01	460.35
	2	10.28	127.23	233.36	300.54	317.84	318.92	353.98	375.17	343.82	347.99	330.78	337.38	332.99	314.67
	3	0.00	238.80	391.08	496.93	456.00	405.66	403.10	354.45	341.59	332.72	335.86	356.96	386.74	369.44
	3	0.00	178.85	238.61	261.60	313.19	405.34	378.42	354.16	335.74	343.32	331.76	360.85	338.15	341.49
	1	0.00	229.28	307.83	378.54	423.01	514.24	567.10	511.19	455.47	445.27	460.56	434.12	452.59	433.62
	3	0.00	243.79	263.93	343.30	356.25	351.84	396.79	395.00	383.28	379.15	406.78	368.15	386.99	406.89
	2	0.00	244.56	331.66	430.38	525.94	487.14	506.36	522.42	500.18	466.81	490.01	457.84	466.42	469.08
	1	0.00	177.70	226.93	274.26	281.36	286.07	313.14	285.64	278.19	281.49	303.36	296.99	288.49	283.64
	2	0.00	214.52	303.38	375.11	434.78	460.50	460.65	389.43	389.19	384.06	384.60	392.86	392.85	387.66

Assay LOQ = 10 ng/mL
(. = no sample analyzed and/or reported)

Appendix III
Individual Subject Plasma Concentrations
Treatment C - Uncoated Capsule + PPI Fasted

		Scheduled Time (h)													
Subject	Period	9.5	10	12	14	16	24	36	48	72	96	120	144	168	192
PPD	2	378.12	340.38	329.38	307.77	300.02	227.34	182.73	136.12	96.11	59.37	39.66	84.79	21.57	13.58
	3	304.27	276.50	273.22	237.39	221.39	168.44	134.43	95.76	56.85	35.40	24.03	16.75	12.92	10.21
	3	375.62	333.90	311.55	266.46	254.40	191.91	139.42	113.03	70.17	42.16	30.55	18.82	15.27	11.38
	1	380.14	360.12	352.32	319.54	283.43	216.70	160.60	123.93	77.34	49.76	33.11	21.40	15.51	12.34
	2	387.36	420.63	400.83	371.53	354.52	282.20	210.81	177.45	125.29	86.81	66.86	49.56	36.86	28.30
	1	377.46	368.36	346.78	314.09	296.17	244.65	184.02	156.60	116.31	82.97	55.69	45.11	36.09	27.35
	2	424.07	374.84	345.94	312.07	295.06	243.41	180.78	140.31	88.17	59.81	42.41	29.24	23.50	17.56
	3	312.16	276.55	257.41	245.59	227.29	178.21	146.10	112.61	73.32	47.69	36.56	25.66	18.57	14.14
	1	397.37	381.58	356.53	325.10	310.16	242.30	195.76	155.76	100.31	66.04	45.65	34.75	27.27	18.52
	1	476.75	475.05	483.18	444.36	411.71	331.55	248.04	191.50	123.79	86.90	60.70	45.69	35.64	27.27
	2	341.95	331.05	310.17	306.04	280.37	222.50	169.94	137.93	89.31	65.79	43.28	36.66	29.13	20.96
	3	371.57	362.27	326.69	303.20	273.45	217.46	179.13	132.44	87.33	51.20	36.17	26.28	19.93	13.58
	3	342.72	331.49	323.28	292.50	285.39	226.62	189.29	150.77	106.33	73.72	51.86	37.92	30.21	22.81
	1	425.94	411.98	383.88	339.51	300.50	227.74	171.68	125.20	82.82	54.73	36.22	26.31	21.26	17.41
	3	371.30	362.04	349.01	289.32	269.58	212.02	166.18	127.70	85.14	59.30	41.62	30.95	22.13	16.00
	2	479.68	447.22	399.67	423.13	370.26	278.32	208.34	156.94	102.21	67.16	45.48	32.12	25.40	21.03
	1	289.70	273.28	251.68	227.71	210.72	158.07	128.40	107.16	69.18	42.79	31.00	22.05	15.82	13.40
	2	427.60	411.21	373.99	342.50	315.24	262.80	197.64	160.18	108.44	76.12	51.59	38.53	28.04	20.71

Assay LOQ = 10 ng/mL
(. = no sample analyzed and/or reported)

Appendix IV
Individual Subject Blood Sampling Times
Treatment A - EC Tablet Fasted

Subject	Period	Scheduled Time (h) 0	1	2	3	3.5	4	4.5	5	6	7	7.5	8	8.5	9
PPD	3	-0.75	1.00	2.00	3.00	3.50	4.00	4.50	5.00	6.00	7.00	7.50	8.00	8.50	9.00
	2	-0.75	1.00	2.00	3.00	3.50	4.00	4.50	5.00	6.00	7.00	7.50	8.00	8.50	9.00
	1	-0.66	1.00	2.00	3.00	3.51	4.01	4.50	5.00	6.01	7.00	7.50	8.00	8.50	9.00
	2	-0.75	1.00	2.00	3.00	3.50	4.00	4.50	5.00	6.00	7.02	7.50	8.00	8.50	9.01
	1	-0.75	1.00	2.00	3.00	3.50	4.00	4.50	5.00	6.00	7.00	7.50	8.00	8.52	9.00
	3	-0.75	1.00	2.00	3.00	3.50	4.00	4.50	5.00	6.00	7.00	7.50	8.03	8.51	9.00
	3	-0.74	1.00	2.00	3.00	3.50	4.00	4.50	5.00	6.00	7.00	7.50	8.00	8.50	9.00
	1	-0.75	1.00	2.00	3.00	3.52	4.00	4.50	5.00	6.00	7.00	7.50	8.01	8.50	9.00
	3	-0.75	1.00	2.00	3.01	3.50	4.00	4.52	5.00	6.00	7.02	7.50	8.00	8.50	9.00
	2	-0.53	1.01	2.12	3.01	3.52	4.00	4.55	5.01	6.00	7.01	7.51	8.11	8.55	9.01
	1	-0.74	1.00	2.00	3.04	3.52	4.04	4.52	5.00	6.00	7.00	7.50	8.02	8.56	9.01
	2	-0.73	1.01	2.01	3.01	3.53	4.00	4.53	5.00	6.00	7.01	7.51	8.01	8.51	9.00
	2	-0.73	1.01	2.01	3.01	3.50	4.00	4.50	5.00	6.00	7.01	7.52	8.01	8.51	9.03
	3	-0.75	1.09	2.01	3.00	3.50	4.00	4.50	5.00	6.00	7.00	7.52	8.01	8.51	9.01
	1	-0.75	1.00	2.00	3.00	3.52	4.00	4.50	5.00	6.00	7.00	7.50	8.03	8.51	9.01
	3	-0.75	1.00	2.00	3.00	3.50	4.00	4.50	5.00	6.00	7.00	7.52	8.01	8.52	9.02
	2	-0.72	1.03	2.00	3.00	3.50	4.00	4.50	5.00	6.00	7.00	7.50	8.03	8.50	9.01
	1	-0.75	1.00	2.00	3.00	3.51	4.00	4.50	5.00	6.00	7.00	7.50	8.01	8.51	9.00

(. = no sample analyzed and/or reported)

Appendix IV
Individual Subject Blood Sampling Times
Treatment A - EC Tablet Fasted

		Scheduled Time (h)													
Subject	Period	9.5	10	12	14	16	24	36	48	72	96	120	144	168	192
PPD	3	9.50	10.00	12.00	14.00	16.00	24.00	36.00	48.00	72.00	96.00	120.00	144.00	168.00	192.00
	2	9.50	10.00	12.14	14.00	16.00	24.01	36.00	48.06	72.00	96.00	120.09	144.00	168.00	192.00
	1	9.52	10.00	12.00	14.00	16.00	24.00	36.01	48.00	72.01	96.00	120.00	144.00	168.00	192.00
	2	9.50	10.01	12.00	14.00	16.00	24.00	36.00	48.01	72.00	96.01	120.09	144.01	168.01	192.01
	1	9.52	10.00	12.00	14.00	16.00	24.00	36.02	48.07	72.00	96.00	120.00	144.00	168.01	192.00
	3	9.50	10.00	12.00	14.05	16.00	24.00	36.05	48.00	72.00	96.00	120.01	144.00	168.00	192.00
	3	9.50	10.00	12.00	14.00	16.00	24.00	36.00	48.00	72.00	96.00	120.00	144.00	168.00	192.00
	1	9.52	10.00	12.00	14.00	16.00	24.00	36.03	48.00	72.00	96.00	120.00	144.00	168.00	192.00
	3	9.50	10.00	12.01	14.00	16.00	24.00	36.00	48.00	72.00	96.00	120.00	144.00	168.00	192.00
	2	9.50	10.01	12.01	14.01	16.01	24.05	36.07	48.11	72.03	96.07	120.09	144.00	168.08	192.51
	1	9.53	10.01	12.00	14.02	16.03	24.01	36.06	48.01	72.00	96.00	120.00	144.00	168.01	192.00
	2	9.50	10.00	12.02	14.01	16.00	24.01	36.02	48.01	72.01	96.02	120.09	144.00	168.01	192.03
	2	9.51	10.03	12.03	14.01	16.00	24.01	36.01	48.01	72.01	96.02	120.09	144.00	168.01	192.03
	3	9.50	10.01	12.00	14.00	16.01	24.02	36.08	48.00	72.01	96.00	120.00	144.00	168.00	192.00
	1	9.53	10.01	12.00	14.02	16.02	24.00	36.00	48.01	72.00	96.00	120.00	144.00	168.01	192.01
	3	9.50	10.00	12.00	14.00	16.00	24.01	36.10	48.00	72.01	96.00	120.00	144.00	168.00	192.00
	2	9.51	10.01	12.15	14.01	16.00	24.04	36.02	48.03	72.01	96.02	120.10	144.00	168.01	192.03
	1	9.53	10.00	12.00	14.02	16.01	24.00	36.10	48.01	72.00	96.00	120.00	144.00	168.03	192.00

(. = no sample analyzed and/or reported)

Appendix IV
Individual Subject Blood Sampling Times
Treatment B - EC Tablet Fed

		Scheduled Time (h)													
Subject	Period	0	1	2	3	3.5	4	4.5	5	6	7	7.5	8	8.5	9
PPD	1	-0.75	1.00	2.00	3.00	3.50	4.00	4.50	5.00	6.00	7.00	7.50	8.00	8.50	9.00
	1	-0.75	1.00	2.00	3.00	3.51	4.00	4.50	5.00	6.01	7.00	7.50	8.00	8.50	9.00
	2	-0.71	1.00	2.01	3.00	3.50	4.00	4.50	5.00	6.00	7.02	7.50	8.01	8.50	9.01
	3	-0.75	1.01	2.01	3.01	3.50	4.01	4.51	5.00	6.00	7.00	7.50	8.01	8.50	9.00
	3	-0.75	1.01	2.01	3.01	3.50	4.00	4.50	5.00	6.00	7.00	7.50	8.01	8.50	9.00
	2	-0.75	1.04	2.00	3.00	3.50	4.00	4.50	5.03	6.00	7.00	7.50	8.00	8.50	9.00
	1	-0.74	1.00	2.00	3.00	3.50	4.00	4.49	5.00	6.00	7.00	7.50	8.00	8.50	9.00
	2	-0.74	1.01	2.00	3.01	3.52	4.00	4.50	5.00	6.00	7.02	7.50	8.00	8.51	9.01
	2	-0.74	1.01	2.00	3.00	3.51	4.00	4.50	5.00	6.00	7.01	7.51	8.00	8.50	9.01
	3	-0.75	1.01	2.15	3.01	3.50	4.17	4.49	5.00	6.00	7.01	7.57	8.19	8.51	9.00
	3	-0.75	1.00	2.01	3.00	3.50	4.00	4.51	5.00	6.00	7.01	7.52	8.01	8.50	9.00
	1	-0.74	1.00	2.00	3.00	3.52	4.01	4.55	5.00	6.00	7.00	7.50	8.02	8.51	9.02
	1	-0.75	1.00	2.00	3.00	3.55	4.01	4.50	5.00	6.00	7.00	7.50	8.02	8.52	9.01
	2	-0.72	1.01	2.01	3.01	3.50	4.00	4.51	5.00	6.00	7.01	7.51	8.00	8.51	9.01
	2	-0.72	1.01	2.00	3.01	3.50	4.00	4.50	5.00	6.00	7.00	7.50	8.00	8.51	9.02
	1	-0.75	1.00	2.00	3.00	3.51	4.00	4.50	5.00	6.00	7.00	7.50	8.01	8.51	9.00
	3	-0.75	1.00	2.00	3.00	3.50	4.00	4.50	5.00	6.00	7.00	7.52	8.01	8.52	9.02
	3	-0.75	1.00	2.00	3.00	3.50	4.00	4.50	5.00	6.00	7.00	7.51	8.01	8.52	9.02

(. = no sample analyzed and/or reported)

Appendix IV
Individual Subject Blood Sampling Times
Treatment B - EC Tablet Fed

		Scheduled Time (h)													
Subject	Period	9.5	10	12	14	16	24	36	48	72	96	120	144	168	192
PPD	1	9.50	10.00	12.00	14.00	16.00	24.00	36.00	48.00	72.00	96.00	120.00	144.00	168.00	192.00
	1	9.51	10.00	12.00	14.00	16.00	24.06	36.00	48.00	72.00	96.00	120.00	144.00	168.00	192.00
	2	9.50	10.01	12.00	14.00	16.00	24.00	36.00	48.01	72.00	96.21	120.09	144.01	168.09	192.00
	3	9.51	10.01	12.08	14.00	16.00	24.00	36.00	48.01	72.01	96.00	120.01	144.01	168.00	192.01
	3	9.50	10.01	12.02	14.00	16.00	24.00	36.05	48.00	72.01	96.00	120.01	144.01	168.00	192.00
	2	9.50	10.00	12.00	14.01	16.02	24.00	36.00	48.00	72.00	96.00	120.07	144.00	168.02	192.01
	1	9.51	10.00	12.00	14.00	16.00	24.00	36.00	48.00	72.00	96.00	120.00	144.00	168.00	192.00
	2	9.50	10.00	12.00	14.01	16.00	24.00	36.02	48.00	72.01	96.00	120.08	144.00	168.00	192.00
	2	9.50	10.01	12.00	14.00	16.01	24.00	36.02	48.00	72.01	96.00	120.08	144.00	168.00	192.00
	3	9.50	10.01	12.00	14.13	16.00	24.00	36.06	48.00	72.01	96.24	120.01	144.00	168.00	192.00
	3	9.50	10.00	12.00	14.00	16.00	24.01	36.01	48.00	72.01	96.00	120.00	144.00	168.00	192.00
	1	9.54	10.06	12.00	14.02	16.02	24.01	36.04	48.01	72.00	96.00	120.00	144.00	168.31	192.00
	1	9.54	10.00	12.00	14.02	16.01	24.00	36.01	48.01	72.00	96.00	120.00	144.00	168.00	192.00
	2	9.51	10.01	12.01	14.01	16.00	24.01	36.03	48.00	72.01	96.02	120.09	144.00	168.01	192.03
	2	9.51	10.01	12.05	14.01	16.00	24.01	36.02	48.00	72.01	96.02	120.09	144.00	168.01	192.03
	1	9.54	10.00	12.00	14.02	16.02	24.00	36.08	48.01	72.00	96.00	120.00	144.00	168.02	192.01
	3	9.50	10.00	12.00	14.00	16.00	24.01	36.03	48.00	72.01	96.00	120.00	144.00	168.00	192.02
	3	9.50	10.00	12.01	14.00	16.00	24.00	36.10	48.00	72.00	96.00	120.00	144.00	168.00	192.01

(. = no sample analyzed and/or reported)

Appendix IV
Individual Subject Blood Sampling Times
Treatment C - Uncoated Capsule + PPI Fasted

		Scheduled Time (h)													
Subject	Period	0	1	2	3	3.5	4	4.5	5	6	7	7.5	8	8.5	9
PPD	2	-0.76	0.99	1.99	2.99	3.49	3.99	4.49	4.99	5.99	6.99	7.49	7.99	8.49	8.99
	3	-0.75	1.00	2.00	3.00	3.50	4.00	4.50	5.00	6.00	7.00	7.50	8.00	8.50	9.00
	3	-0.64	1.06	2.06	3.08	3.55	4.01	4.50	5.00	6.00	7.00	7.50	8.00	8.70	9.00
	1	-0.74	1.00	2.00	3.00	3.50	4.01	4.50	5.00	6.00	7.00	7.50	8.00	8.50	9.00
	2	-0.75	1.00	2.00	3.00	3.50	4.00	4.50	5.00	6.00	7.04	7.50	8.00	8.50	9.01
	1	-0.77	1.00	2.02	3.00	3.50	4.00	4.50	5.00	6.00	7.00	7.50	8.00	8.50	9.00
	2	-0.75	1.00	2.00	3.00	3.55	4.00	4.50	5.00	6.00	7.02	7.56	8.00	8.50	9.02
	3	-0.75	1.00	2.00	3.00	3.50	4.00	4.50	5.00	6.00	7.00	7.50	8.00	8.50	9.00
	1	-0.75	1.00	2.00	3.00	3.51	4.14	4.51	5.00	6.00	7.00	7.50	8.15	8.50	9.00
	1	-0.66	1.04	2.05	3.11	3.57	4.09	4.52	5.15	6.00	7.04	7.50	8.01	8.51	9.01
	2	-0.73	1.01	2.01	3.01	3.52	4.00	4.51	5.00	6.00	7.01	7.51	8.02	8.51	9.00
	3	-0.75	1.00	2.01	3.00	3.50	4.01	4.51	5.00	6.00	7.01	7.51	8.19	8.53	9.03
	3	-0.75	1.00	2.01	3.04	3.50	4.00	4.50	5.00	6.00	7.01	7.54	8.01	8.51	9.01
	1	-0.75	1.01	2.00	3.00	3.52	4.00	4.50	5.00	6.00	7.00	7.50	8.02	8.51	9.01
	3	-0.75	1.00	2.01	3.00	3.50	4.01	4.50	5.00	6.00	7.00	7.52	8.01	8.55	9.02
	2	-0.72	1.01	2.00	3.01	3.50	4.00	4.50	5.00	6.00	7.00	7.50	8.00	8.50	9.02
	1	-0.75	1.00	2.00	3.00	3.51	4.00	4.50	5.00	6.00	7.00	7.50	8.01	8.51	9.00
	2	-0.72	1.03	2.00	3.00	3.50	4.00	4.50	5.00	6.00	7.00	7.50	8.00	8.50	9.01

(. = no sample analyzed and/or reported)

Appendix IV
Individual Subject Blood Sampling Times
Treatment C - Uncoated Capsule + PPI Fasted

		Scheduled Time (h)													
Subject	Period	9.5	10	12	14	16	24	36	48	72	96	120	144	168	192
PPD	3	9.50	10.00	12.00	14.00	16.00	24.00	36.00	48.00	72.00	96.00	120.00	144.00	168.00	192.00
	2	9.50	10.00	12.14	14.00	16.00	24.01	36.00	48.06	72.00	96.00	120.09	144.00	168.00	192.00
	1	9.52	10.00	12.00	14.00	16.00	24.00	36.01	48.00	72.01	96.00	120.00	144.00	168.00	192.00
	2	9.50	10.01	12.00	14.00	16.00	24.00	36.00	48.01	72.00	96.01	120.09	144.01	168.01	192.01
	1	9.52	10.00	12.00	14.00	16.00	24.00	36.02	48.07	72.00	96.00	120.00	144.00	168.01	192.00
	3	9.50	10.00	12.00	14.05	16.00	24.00	36.05	48.00	72.00	96.00	120.01	144.00	168.00	192.00
	3	9.50	10.00	12.00	14.00	16.00	24.00	36.00	48.00	72.00	96.00	120.00	144.00	168.00	192.00
	1	9.52	10.00	12.00	14.00	16.00	24.00	36.03	48.00	72.00	96.00	120.00	144.00	168.00	192.00
	3	9.50	10.00	12.01	14.00	16.00	24.00	36.00	48.00	72.00	96.00	120.00	144.00	168.00	192.00
	2	9.50	10.01	12.01	14.01	16.01	24.05	36.07	48.11	72.03	96.07	120.09	144.00	168.08	192.51
	1	9.53	10.01	12.00	14.02	16.03	24.01	36.06	48.01	72.00	96.00	120.00	144.00	168.01	192.00
	2	9.50	10.00	12.02	14.01	16.00	24.01	36.02	48.01	72.01	96.02	120.09	144.00	168.01	192.03
	2	9.51	10.03	12.03	14.01	16.00	24.01	36.01	48.01	72.01	96.02	120.09	144.00	168.01	192.03
	3	9.50	10.01	12.00	14.00	16.01	24.02	36.08	48.00	72.01	96.00	120.00	144.00	168.00	192.00
	1	9.53	10.01	12.00	14.02	16.02	24.00	36.00	48.01	72.00	96.00	120.00	144.00	168.01	192.01
	3	9.50	10.00	12.00	14.00	16.00	24.01	36.10	48.00	72.01	96.00	120.00	144.00	168.00	192.00
	2	9.51	10.01	12.15	14.01	16.00	24.04	36.02	48.03	72.01	96.02	120.10	144.00	168.01	192.03
	1	9.53	10.00	12.00	14.02	16.01	24.00	36.10	48.01	72.00	96.00	120.00	144.00	168.03	192.00

(. = no sample analyzed and/or reported)

Appendix V
Descriptive Statistics for Plasma Concentrations

Treatment	Scheduled Time (h)	N	Arithmetic Mean	Arithmetic Standard Error	Arithmetic CV (%)	Geometric Mean	Geometric CV (%)	Minimum	Median	Maximum
EC Tablet Fasted	0.0	18	0.00	0.00	.	.	.	0.00	0.00	0.00
	1.0	18	81.86	15.05	77.98	92.35	60.53	0.00	91.66	216.94
	2.0	18	182.41	19.36	45.02	175.93	53.28	0.00	201.62	291.58
	3.0	18	270.36	24.09	37.80	245.17	54.51	56.51	300.58	441.89
	3.5	18	299.14	26.82	38.04	270.50	55.52	62.06	309.38	429.67
	4.0	18	310.54	25.40	34.70	289.36	42.88	121.48	324.55	478.14
	4.5	18	342.70	24.25	30.02	326.06	35.03	147.29	356.11	533.87
	5.0	18	324.28	21.12	27.63	311.24	31.41	144.71	328.52	483.43
	6.0	18	330.35	21.16	27.17	316.70	32.59	127.97	339.31	483.92
	7.0	18	324.84	21.88	28.57	309.69	35.06	115.04	341.47	466.89
	7.5	18	324.69	21.45	28.03	310.16	34.26	116.83	332.96	471.67
	8.0	18	325.89	22.05	28.70	310.12	36.04	112.36	334.34	464.76
	8.5	18	318.34	20.98	27.96	304.37	33.76	117.64	326.48	484.69
	9.0	18	319.63	20.53	27.25	304.95	35.54	105.05	336.89	467.48
	9.5	18	329.17	22.02	28.39	313.74	35.40	112.76	344.61	483.93
	10.0	18	307.40	20.74	28.62	292.17	36.87	99.92	320.91	445.84
	12.0	18	289.40	20.69	30.33	273.61	38.60	95.51	307.20	441.49
	14.0	18	264.88	19.12	30.63	250.19	38.89	88.90	270.97	397.88
	16.0	18	247.80	18.48	31.63	232.93	40.76	79.60	264.01	371.79
	24.0	18	189.73	14.98	33.50	176.90	43.65	60.92	205.11	294.46
	36.0	18	144.48	11.63	34.15	133.98	45.73	47.59	156.72	217.24
	48.0	18	114.28	10.06	37.35	104.37	50.83	35.30	122.84	177.90
	72.0	18	74.04	7.16	41.04	66.50	55.59	21.94	78.14	115.16
	96.0	18	50.30	4.99	42.13	44.85	57.95	14.71	53.29	82.92
	120.0	18	36.09	3.58	42.07	32.33	56.16	10.78	37.58	65.42
	144.0	18	25.09	3.03	51.17	26.48	40.61	0.00	27.74	48.90
	168.0	18	18.54	2.41	55.12	21.44	28.93	0.00	21.13	36.43
	192.0	18	14.04	2.07	62.67	17.50	25.95	0.00	15.23	29.78

Geometric mean and CV were not calculated if all values were <LOQ
Subject PPD Period 2, EC Tablet Fed, had a C(0) >= LOQ and >= 5% of Cmax and is excluded from the descriptive statistics.

Appendix V
Descriptive Statistics for Plasma Concentrations

Treatment	Scheduled Time (h)	N	Arithmetic Mean	Arithmetic Standard Error	Arithmetic CV (%)	Geometric Mean	Geometric CV (%)	Minimum	Median	Maximum
EC Tablet Fed	0.0	17	0.00	0.00	.	.	.	0.00	0.00	0.00
	1.0	17	33.39	9.69	119.66	38.03	105.08	0.00	17.63	122.88
	2.0	17	80.25	18.74	96.30	76.30	119.59	0.00	62.27	223.00
	3.0	17	121.06	24.10	82.07	104.20	101.13	0.00	81.62	295.07
	3.5	17	144.02	27.38	78.39	125.02	101.16	0.00	103.86	338.70
	4.0	17	150.94	28.60	78.13	132.02	97.60	0.00	122.75	365.88
	4.5	17	161.07	29.70	76.01	144.91	88.26	0.00	137.05	386.35
	5.0	17	157.43	27.02	70.76	113.75	117.40	12.85	130.62	369.95
	6.0	17	161.16	25.06	64.12	125.81	93.17	21.31	136.16	362.28
	7.0	17	163.23	24.69	62.38	129.52	87.59	26.61	125.60	355.71
	7.5	17	160.05	24.60	63.37	127.12	86.46	27.15	124.38	357.16
	8.0	17	158.82	25.02	64.95	124.80	88.86	26.70	121.14	362.04
	8.5	17	151.68	23.78	64.65	119.71	87.91	24.40	112.86	351.14
	9.0	17	150.80	24.12	65.95	118.01	89.98	23.84	118.34	361.03
	9.5	17	149.23	24.67	68.16	115.88	91.40	22.74	119.70	387.75
	10.0	17	137.83	22.91	68.53	106.54	92.83	20.35	112.78	361.80
	12.0	17	123.76	21.65	72.13	92.96	100.39	15.83	104.55	336.48
	14.0	17	109.98	19.25	72.15	81.35	105.94	12.49	95.49	287.92
	16.0	17	95.94	17.72	76.18	79.68	86.97	0.00	83.22	271.27
	24.0	17	70.46	13.43	78.60	57.43	91.87	0.00	59.42	205.55
	36.0	17	50.22	10.52	86.33	39.03	102.04	0.00	36.81	164.40
	48.0	17	38.07	8.02	86.84	33.62	85.70	0.00	28.19	123.25
	72.0	17	23.88	5.35	92.33	26.27	66.86	0.00	17.43	81.51
	96.0	17	15.08	3.47	94.78	21.20	48.34	0.00	12.95	46.99
	120.0	17	10.86	2.60	98.70	17.34	38.81	0.00	11.03	31.11
	144.0	17	6.52	2.06	130.16	15.31	28.41	0.00	0.00	22.42
	168.0	17	4.75	1.64	142.69	13.25	19.31	0.00	0.00	16.87
	192.0	17	3.08	1.40	187.00	13.05	11.52	0.00	0.00	14.61

Geometric mean and CV were not calculated if all values were <LOQ
Subject PPD Period 2, EC Tablet Fed, had a C(0) >= LOQ and >= 5% of Cmax and is excluded from the descriptive statistics.

Appendix V
Descriptive Statistics for Plasma Concentrations

Treatment	Scheduled Time (h)	N	Arithmetic Mean	Arithmetic Standard Error	Arithmetic CV (%)	Geometric Mean	Geometric CV (%)	Minimum	Median	Maximum
Uncoated Capsule + PPI Fasted	0.0	18	0.57	0.57	424.26	10.28	.	0.00	0.00	10.28
	1.0	18	207.87	10.32	21.07	203.45	21.81	127.23	203.70	292.36
	2.0	18	302.26	12.64	17.74	297.80	17.91	226.09	302.76	414.18
	3.0	18	372.60	14.83	16.88	367.45	17.47	261.60	373.18	496.93
	3.5	18	390.04	14.64	15.92	385.41	16.02	281.36	383.33	525.94
	4.0	18	400.26	15.18	16.09	395.34	16.37	286.07	401.09	514.24
	4.5	18	424.85	17.35	17.33	418.94	17.33	313.14	420.93	567.10
	5.0	18	395.88	15.74	16.87	390.66	16.86	285.64	390.05	522.42
	6.0	18	384.51	13.92	15.36	380.26	15.47	278.19	386.99	500.18
	7.0	18	377.58	12.56	14.11	374.05	14.22	281.49	377.80	484.56
	7.5	18	375.58	13.13	14.83	371.75	14.79	291.78	377.98	490.01
	8.0	18	372.67	11.39	12.97	369.69	13.17	296.67	371.46	457.84
	8.5	18	378.41	12.10	13.56	375.07	13.87	288.49	384.04	466.42
	9.0	18	373.10	12.47	14.18	369.52	14.44	283.64	375.52	469.08
	9.5	18	381.32	12.45	13.85	377.85	14.03	289.70	377.79	479.68
	10.0	18	363.25	13.36	15.60	359.02	15.96	273.28	362.16	475.05
	12.0	18	343.08	13.11	16.21	338.90	16.23	251.68	346.36	483.18
	14.0	18	314.88	13.45	18.12	310.20	17.85	227.71	309.92	444.36
	16.0	18	292.20	11.95	17.35	288.16	17.26	210.72	290.22	411.71
	24.0	18	229.57	10.04	18.55	225.89	18.70	158.07	226.98	331.55
	36.0	18	177.41	7.05	16.86	175.04	17.05	128.40	179.96	248.04
	48.0	18	138.97	5.88	17.96	136.86	18.21	95.76	137.02	191.50
	72.0	18	92.13	4.55	20.97	90.18	21.81	56.85	88.74	125.29
	96.0	18	61.54	3.65	25.17	59.66	26.41	35.40	59.59	86.90
	120.0	18	42.91	2.63	25.98	41.57	26.56	24.03	42.01	66.86
	144.0	18	34.59	3.69	45.29	32.00	40.74	16.75	31.53	84.79
	168.0	18	24.17	1.75	30.79	23.08	32.43	12.92	22.81	36.86
	192.0	18	18.14	1.33	31.18	17.33	31.86	10.21	17.48	28.30

Geometric mean and CV were not calculated if all values were <LOQ
Subject PPD Period 2, EC Tablet Fed, had a C(0) >= LOQ and >= 5% of Cmax and is excluded from the descriptive statistics.

Appendix VI
Individual Subject Pharmacokinetic Parameters
Treatment A - EC Tablet Fasted

Subject	Period	Lag Time* (h)	CMAX (ng/mL)	TMAX (h)	AUC(0-t) (hxng/mL)	AUC(inf) (hxng/mL)	% AUC Extrap	Regression Start Time Nominal	Regression Start Time Actual	Final Time C>=LOQ	No. Points in Regr	Regr r^2	Lambda_z (/h)	t½ (h)	CL/F (L/h)	Vz/F (L)
PPD	3	.	147.29	4.50	4,857.67	5,511.14	11.9	47.00	48.00	120.00	4	0.9915	0.01649	42.03	2.415	146.42
	2	.	269.11	8.50	11,565.25	12,455.79	7.1	71.00	72.00	168.00	5	0.9879	0.01444	48.01	1.068	74.02
	1	.	278.51	4.50	7,607.44	8,260.34	7.9	47.00	48.00	120.00	4	0.9912	0.01954	35.47	1.611	82.45
	2	.	441.89	3.00	16,120.60	17,169.64	6.1	47.00	48.01	192.01	7	0.9788	0.01418	48.88	0.775	54.66
	1	3.00	397.87	7.50	18,547.33	19,815.71	6.4	48.00	48.07	192.00	7	0.9981	0.01406	49.30	0.672	47.77
	3	.	450.27	4.50	22,675.96	25,209.09	10.0	36.00	36.05	192.00	8	0.9973	0.01175	58.97	0.528	44.91
	3	.	483.93	9.50	22,738.24	24,182.85	6.0	36.00	36.00	192.00	8	0.9910	0.01476	46.96	0.550	37.29
	1	.	411.20	3.52	19,268.61	20,226.41	4.7	23.00	24.00	192.00	9	0.9983	0.01587	43.69	0.658	41.47
	3	2.00	450.94	6.00	18,755.35	19,781.67	5.2	72.00	72.00	192.00	6	0.9926	0.01456	47.62	0.673	46.22
	2	.	424.72	4.55	16,498.83	18,491.08	10.8	96.00	96.07	192.51	5	0.9952	0.00974	71.13	0.720	73.86
	1	.	382.79	9.53	19,676.87	21,468.36	8.3	36.00	36.06	192.00	8	0.9879	0.01315	52.69	0.620	47.13
	2	.	445.60	4.53	18,779.74	19,761.83	5.0	36.00	36.02	192.03	8	0.9910	0.01573	44.07	0.673	42.82
	2	.	370.37	9.51	19,630.94	20,973.13	6.4	36.00	36.01	192.03	8	0.9896	0.01441	48.09	0.635	44.02
	3	.	392.60	4.00	14,002.34	15,276.58	8.3	95.00	96.00	192.00	5	0.9508	0.01078	64.31	0.871	80.83
	1	.	355.54	6.00	11,500.16	12,493.18	7.9	95.00	96.00	192.01	5	0.9979	0.01105	62.72	1.065	96.40
	3	2.00	219.93	7.52	6,732.08	7,574.44	11.1	72.00	72.01	144.00	4	0.9866	0.01201	57.70	1.757	146.27
	2	.	312.57	4.50	15,414.33	16,514.39	6.7	36.00	36.02	192.03	8	0.9886	0.01387	49.98	0.806	58.11
	1	2.00	533.87	4.50	24,102.97	25,484.26	5.4	36.00	36.10	192.00	8	0.9947	0.01522	45.54	0.522	34.31

(. = parameter could not be estimated)
*A lag time was not calculated if the first concentration >= LOQ occurred at the first sample time.

Appendix VI
Individual Subject Pharmacokinetic Parameters
Treatment B - EC Tablet Fed

Subject	Period	Lag Time* (h)	CMAX (ng/mL)	TMAX (h)	AUC(0-t) (hxng/mL)	AUC(inf) (hxng/mL)	% AUC Extrap	Regression Start Time Nominal	Regression Start Time Actual	Final Time C>=LOQ	No. Points in Regr	Regr r^2	Lambda_z (/h)	t½ (h)	CL/F (L/h)	Vz/F (L)
PPD	1	5.00	27.15	7.50	182.90	279.12	34.5	9.00	9.50	14.00	4	0.9938	0.12981	5.34	47.68	367.33
	1	2.00	144.33	4.50	2,875.23	3,402.37	15.5	35.00	36.00	72.00	3	0.9942	0.02326	29.80	3.912	168.16
	2	3.00	71.48	4.50	1,399.14	1,719.88	18.6	16.00	16.00	48.01	4	0.9594	0.03703	18.72	7.738	208.96
	3	.	387.75	9.51	17,013.40	17,986.46	5.4	72.00	72.01	192.01	6	0.9690	0.01449	47.83	0.740	51.06
	3	.	75.27	7.00	1,609.92	.	.	.	.	72.01	.	.	.	.	.	.
	2	.	30.39	8.00	2,549.77	4,919.52	48.2	35.00	36.00	168.02	7	0.9893	0.00433	160.09	2.705	624.84
	1	.	45.72	7.00	763.11	1,018.73	25.1	15.00	16.00	36.00	3	0.9875	0.03948	17.56	13.06	330.94
	2	.	278.69	3.52	7,424.04	8,387.45	11.5	47.00	48.00	168.00	6	0.9627	0.01195	57.98	1.587	132.74
	2	5.00	315.30	8.00	11,538.14	12,881.72	10.4	72.00	72.01	192.00	6	0.9511	0.01087	63.75	1.033	95.02
	3	2.15	250.60	7.01	8,727.92	9,907.93	11.9	72.00	72.01	192.00	6	0.9625	0.00970	71.44	1.343	138.45
	3	.	73.25	6.00	2,726.49	.	.	.	.	120.00	.	.	.	.	.	.
	1	3.00	314.87	4.55	9,902.21	10,528.76	6.0	48.00	48.01	168.31	6	0.9841	0.01609	43.08	1.264	78.56
	1	.	256.51	4.50	7,173.81	7,909.66	9.3	48.00	48.01	144.00	5	0.9857	0.01477	46.92	1.683	113.89
	2	.	137.05	4.51	4,203.47	4,942.40	15.0	36.00	36.03	96.02	4	0.9850	0.01752	39.56	2.693	153.70
	2	.	87.43	4.50	1,608.05	2,098.59	23.4	24.00	24.01	48.00	3	0.9518	0.02677	25.90	6.342	236.93
	1	.	272.07	4.50	6,764.53	7,554.08	10.5	48.00	48.01	120.00	4	0.9760	0.01567	44.23	1.762	112.43
	3	.	108.85	7.00	3,163.41	4,253.62	25.6	48.00	48.00	120.00	4	0.9562	0.00964	71.89	3.129	324.50
	3	.	325.45	4.50	10,511.03	11,730.88	10.4	72.00	72.00	192.01	6	0.9850	0.01007	68.83	1.135	112.66

(. = parameter could not be estimated)
*A lag time was not calculated if the first concentration >= LOQ occurred at the first sample time.

Appendix VI
Individual Subject Pharmacokinetic Parameters
Treatment C - Uncoated Capsule + PPI Fasted

Subject	Period	Lag Time* (h)	CMAX (ng/mL)	TMAX (h)	AUC(0-t) (hxng/mL)	AUC(inf) (hxng/mL)	% AUC Extrap	Regression Start Time Nominal	Regression Start Time Actual	Final Time C>=LOQ	No. Points in Regr	Regr r^2	Lambda_z (/h)	t½ (h)	CL/F (L/h)	Vz/F (L)
PPD	2	.	445.77	2.99	20,896.85	.	.	.	.	191.99	.	.	.	.	.	.
	3	.	353.87	3.50	13,764.48	14,481.24	4.9	72.00	72.00	192.00	6	0.9832	0.01425	48.65	0.919	64.50
	3	.	447.08	4.50	16,092.90	16,804.88	4.2	48.00	48.00	192.10	7	0.9851	0.01599	43.36	0.792	49.54
	1	.	460.34	4.50	17,746.68	18,479.64	4.0	35.00	36.00	192.00	8	0.9913	0.01683	41.18	0.720	42.78
	2	.	420.63	10.01	24,901.94	27,095.86	8.1	36.00	36.03	192.01	8	0.9972	0.01290	53.74	0.491	38.08
	1	.	402.97	4.50	22,358.35	24,570.85	9.0	36.00	36.00	192.01	8	0.9932	0.01236	56.07	0.542	43.81
	2	.	459.34	4.50	19,914.87	21,093.09	5.6	35.00	36.00	192.00	8	0.9884	0.01490	46.51	0.631	42.34
	3	.	367.72	4.50	15,920.08	16,873.34	5.6	36.00	36.04	192.00	8	0.9921	0.01484	46.71	0.789	53.16
	1	.	477.57	3.51	21,464.59	22,684.16	5.4	23.00	24.00	192.00	9	0.9913	0.01519	45.64	0.587	38.63
	1	.	566.16	4.52	27,087.62	29,032.66	6.7	36.00	36.15	192.08	8	0.9877	0.01402	49.43	0.458	32.69
	2	.	375.17	5.00	19,190.70	20,783.64	7.7	36.00	36.02	192.01	8	0.9857	0.01316	52.69	0.640	48.68
	3	.	496.93	3.00	18,655.05	19,475.16	4.2	24.00	24.00	192.00	9	0.9905	0.01656	41.85	0.683	41.26
	3	.	405.34	4.00	20,677.13	22,327.76	7.4	24.00	24.00	192.00	9	0.9941	0.01382	50.15	0.596	43.13
	1	.	567.10	4.50	19,428.23	20,907.70	7.1	95.00	96.00	192.01	5	0.9743	0.01177	58.91	0.637	54.10
	3	.	406.89	9.02	18,674.17	19,730.51	5.4	24.00	24.01	192.00	9	0.9945	0.01514	45.78	0.675	44.55
	2	.	525.94	3.50	23,040.95	24,447.55	5.8	36.00	36.04	192.03	8	0.9818	0.01495	46.37	0.544	36.42
	1	.	313.14	4.50	14,392.65	15,267.89	5.7	23.00	24.00	192.00	9	0.9896	0.01531	45.28	0.872	56.94
	2	.	460.65	4.50	22,362.06	23,751.30	5.8	24.00	24.00	192.03	9	0.9949	0.01490	46.51	0.560	37.60

(. = parameter could not be estimated)
*A lag time was not calculated if the first concentration >= LOQ occurred at the first sample time.

Appendix VII
Descriptive Statistics for Pharmacokinetic Parameters

				Arithmetic			Geometric				
Treatment	Parameter	Units	N	Mean	Standard Deviation	CV (%)	Mean	CV (%)	Minimum	Median	Maximum
EC Tablet Fasted	TLAG	h	4	2.2513	0.5012	22.26	.	.	1.9994	2.0014	3.0031
	CMAX	ng/mL	18	376.0559	98.0308	26.07	360.8826	32.53	147.2910	395.2374	533.8655
	TMAX	h	18	5.8976	2.2000	37.30	.	.	3.0036	4.5407	9.5333
	AUC(0-t)	hxng/mL	18	16,026.3726	5,635.0075	35.16	14,790.8396	47.45	4,857.6726	17,523.0845	24,102.9710
	AUC(inf)	hxng/mL	18	17,258.3266	5,955.0054	34.51	15,997.7562	45.74	5,511.1409	19,126.4525	25,484.2642
	Lambda_z	/h	18	0.0140	0.0023	16.74	0.0138	17.10	0.0097	0.0143	0.0195
	t½	h	18	50.9539	8.8704	17.41	50.2559	17.10	35.4694	48.4814	71.1336
	CL/F	L/h	18	0.9233	0.5090	55.13	0.8319	45.74	0.5222	0.6966	2.4149
	Vz/F	L	18	66.6092	33.9633	50.99	60.3180	45.88	34.3132	51.2159	146.4164
EC Tablet Fed	TLAG	h	6	3.3586	1.3386	39.86	.	.	1.9994	3.0015	5.0017
	CMAX	ng/mL	17	186.5738	117.6370	63.05	145.1312	94.12	27.1480	144.3250	387.7480
	TMAX	h	17	5.8001	1.6925	29.18	.	.	3.5161	4.5542	9.5056
	AUC(0-t)	hxng/mL	17	5,740.3997	4,680.9190	81.54	3,635.5289	170.21	182.9003	4,203.4749	17,013.3966
	AUC(inf)	hxng/mL	15	6,973.4432	5,065.3161	72.64	4,654.6700	160.02	279.1198	7,554.0780	17,986.4628
	Lambda_z	/h	15	0.0258	0.0303	117.32	0.0189	79.66	0.0096	0.0157	0.1298
	t½	h	15	43.5216	20.9345	48.10	36.7348	79.66	5.3398	44.2336	71.8877
	CL/F	L/h	15	6.3404	11.9177	187.96	2.8593	160.02	0.7399	1.7618	47.6820
	Vz/F	L	15	175.0215	98.1477	56.08	151.5334	60.81	51.0613	138.4459	367.3285
Uncoated Capsule + PPI Fasted	TLAG	h	0	.	.	.	.	.	.	.	.
	CMAX	ng/mL	18	441.8128	69.5915	15.75	436.6144	16.01	313.1404	446.4265	567.1021
	TMAX	h	18	4.7257	1.8443	39.03	.	.	2.9919	4.4997	10.0092
	AUC(0-t)	hxng/mL	18	19,809.4048	3,508.5981	17.71	19,511.1356	18.23	13,764.4776	19,671.5530	27,087.6171
	AUC(inf)	hxng/mL	17	21,047.4835	4,021.6837	19.11	20,682.9228	19.58	14,481.2370	20,907.7004	29,032.6560
	Lambda_z	/h	17	0.0145	0.0014	9.62	0.0145	9.88	0.0118	0.0149	0.0168
	t½	h	17	48.1660	4.8635	10.10	47.9431	9.88	41.1780	46.5084	58.9137
	CL/F	L/h	17	0.6551	0.1293	19.74	0.6435	19.58	0.4584	0.6366	0.9190
	Vz/F	L	17	45.1889	8.3112	18.39	44.5075	17.94	32.6936	43.1304	64.4999

Geometric mean and CV were not calculated for Tmax or Tlag.
Subject PPD Period 2, EC Tablet Fed, had a C(0) >= LOQ and >= 5% of Cmax and is excluded from the descriptive statistics.

Appendix VIII
Statistical Analysis of Pharmacokinetic Parameters

---------- ASSAY=Total Molybdenum ----------

The GLM Procedure

Class Level Information

Class	Levels	Values
SUBJECT	18	PPD
PERIOD	3	1 2 3
TREATMENT	3	A B C
SEQUENCE	6	ABC ACB BAC BCA CAB CBA

Data for Analysis of LNCMAX LNAUCT

Number of Observations Read	53
Number of Observations Used	53

Data for Analysis of LNAUC

Number of Observations Read	53
Number of Observations Used	50

NOTE: Variables in each group are consistent with respect to the presence or absence of missing values.

LNCMAX = ln(Cmax); LNAUCT = ln[AUC(0-t)]; LNAUC = ln[AUC(inf)].
tment A - EC Tablet Fasted; Treatment B - EC Tablet Fed; Treatment C - Uncoated Capsule + PPI Fasted
Subject PPD Period 2, EC Tablet Fed, had a C(0) >= LOQ and >= 5% of Cmax and is excluded from the statistical analyses.

Appendix VIII
Statistical Analysis of Pharmacokinetic Parameters

---------- ASSAY=Total Molybdenum ----------

The GLM Procedure

Dependent Variable: LNCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	21	17.88490026	0.85166192	4.11	0.0002
Error	31	6.42240550	0.20717437		
Corrected Total	52	24.30730576			

R-Square	Coeff Var	Root MSE	LNCMAX Mean
0.735783	8.040249	0.455164	5.661070

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQUENCE	5	1.74914402	0.34982880	1.69	0.1668
SUBJECT(SEQUENCE)	12	4.05190490	0.33765874	1.63	0.1341
PERIOD	2	0.02154484	0.01077242	0.05	0.9494
TREATMENT	2	11.60818873	5.80409436	28.02	<.0001

Tests of Hypotheses Using the Type III MS for SUBJECT(SEQUENCE) as an Error Term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQUENCE	5	1.74914402	0.34982880	1.04	0.4401

Parameter	Estimate	Standard Error	t Value	Pr > |t|
B-A	-0.90419611	0.15523662	-5.82	<.0001
A-C	-0.19049775	0.15172137	-1.26	0.2187

LNCMAX = ln(Cmax); LNAUCT = ln[AUC(0-t)]; LNAUC = ln[AUC(inf)].
tment A - EC Tablet Fasted; Treatment B - EC Tablet Fed; Treatment C - Uncoated Capsule + PPI Fasted
Subject PPD Period 2, EC Tablet Fed, had a C(0) >= LOQ and >= 5% of Cmax and is excluded from the statistical analyses.

Appendix VIII
Statistical Analysis of Pharmacokinetic Parameters

---------- ASSAY=Total Molybdenum ----------

The GLM Procedure

Dependent Variable: LNAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	21	40.44238385	1.92582780	4.43	<.0001
Error	31	13.46679128	0.43441262		
Corrected Total	52	53.90917513			

R-Square	Coeff Var	Root MSE	LNAUCT Mean
0.750195	7.128694	0.659100	9.245731

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQUENCE	5	5.15134533	1.03026907	2.37	0.0621
SUBJECT(SEQUENCE)	12	6.80651709	0.56720976	1.31	0.2646
PERIOD	2	0.40445189	0.20222595	0.47	0.6321
TREATMENT	2	26.68046366	13.34023183	30.71	<.0001

Tests of Hypotheses Using the Type III MS for SUBJECT(SEQUENCE) as an Error Term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQUENCE	5	5.15134533	1.03026907	1.82	0.1840

Parameter	Estimate	Standard Error	t Value	Pr > |t|
B-A	-1.37848178	0.22479020	-6.13	<.0001
A-C	-0.27697732	0.21969995	-1.26	0.2168

LNCMAX = ln(Cmax); LNAUCT = ln[AUC(0-t)]; LNAUC = ln[AUC(inf)].
tment A - EC Tablet Fasted; Treatment B - EC Tablet Fed; Treatment C - Uncoated Capsule + PPI Fasted
Subject PPD Period 2, EC Tablet Fed, had a C(0) >= LOQ and >= 5% of Cmax and is excluded from the statistical analyses.

Appendix VIII
Statistical Analysis of Pharmacokinetic Parameters

---------- ASSAY=Total Molybdenum ----------

The GLM Procedure
Least Squares Means

TREATMENT	LNCMAX LSMEAN
A	5.88855268
B	4.98435657
C	6.07905043

TREATMENT	LNAUCT LSMEAN
A	9.60176332
B	8.22328154
C	9.87874064

LNCMAX = ln(Cmax); LNAUCT = ln[AUC(0-t)]; LNAUC = ln[AUC(inf)].
tment A - EC Tablet Fasted; Treatment B - EC Tablet Fed; Treatment C - Uncoated Capsule + PPI Fasted
Subject PPD Period 2, EC Tablet Fed, had a C(0) >= LOQ and >= 5% of Cmax and is excluded from the statistical analyses.

Appendix VIII
Statistical Analysis of Pharmacokinetic Parameters

---------- ASSAY=Total Molybdenum ----------

The GLM Procedure

Dependent Variable: LNAUC

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	21	34.11877540	1.62470359	6.09	<.0001
Error	28	7.47080100	0.26681432		
Corrected Total	49	41.58957641			

R-Square	Coeff Var	Root MSE	LNAUC Mean
0.820368	5.496773	0.516541	9.397163

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQUENCE	5	7.44208565	1.48841713	5.58	0.0011
SUBJECT(SEQUENCE)	12	7.76118463	0.64676539	2.42	0.0263
PERIOD	2	0.59316463	0.29658231	1.11	0.3431
TREATMENT	2	14.44787685	7.22393843	27.07	<.0001

Tests of Hypotheses Using the Type III MS for SUBJECT(SEQUENCE) as an Error Term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQUENCE	5	7.44208565	1.48841713	2.30	0.1100

Parameter	Estimate	Standard Error	t Value	Pr > |t|
B-A	-1.14888271	0.18557883	-6.19	<.0001
A-C	-0.13736930	0.17620792	-0.78	0.4422

LNCMAX = ln(Cmax); LNAUCT = ln[AUC(0-t)]; LNAUC = ln[AUC(inf)].
tment A - EC Tablet Fasted; Treatment B - EC Tablet Fed; Treatment C - Uncoated Capsule + PPI Fasted
Subject PPD Period 2, EC Tablet Fed, had a C(0) >= LOQ and >= 5% of Cmax and is excluded from the statistical analyses.

Appendix VIII
Statistical Analysis of Pharmacokinetic Parameters

---------- ASSAY=Total Molybdenum ----------

The GLM Procedure
Least Squares Means

TREATMENT	LNAUC LSMEAN
A	9.68020375
B	8.53132104
C	9.81757305

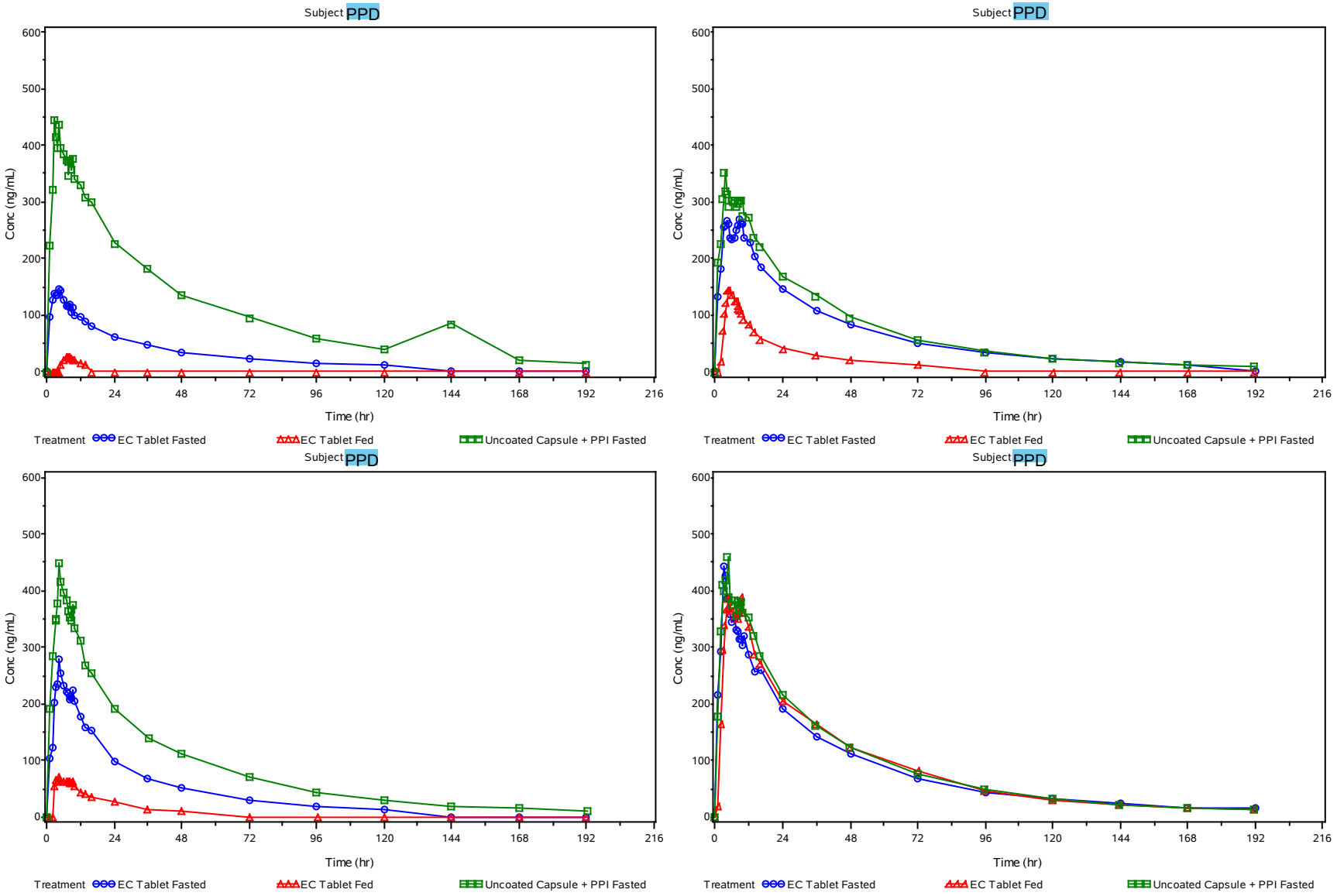
LNCMAX = ln(Cmax); LNAUCT = ln[AUC(0-t)]; LNAUC = ln[AUC(inf)].
tment A - EC Tablet Fasted; Treatment B - EC Tablet Fed; Treatment C - Uncoated Capsule + PPI Fasted
Subject PPD Period 2, EC Tablet Fed, had a C(0) >= LOQ and >= 5% of Cmax and is excluded from the statistical analyses.

Appendix VII
Statistical Analysis of Pharmacokinetic Parameters

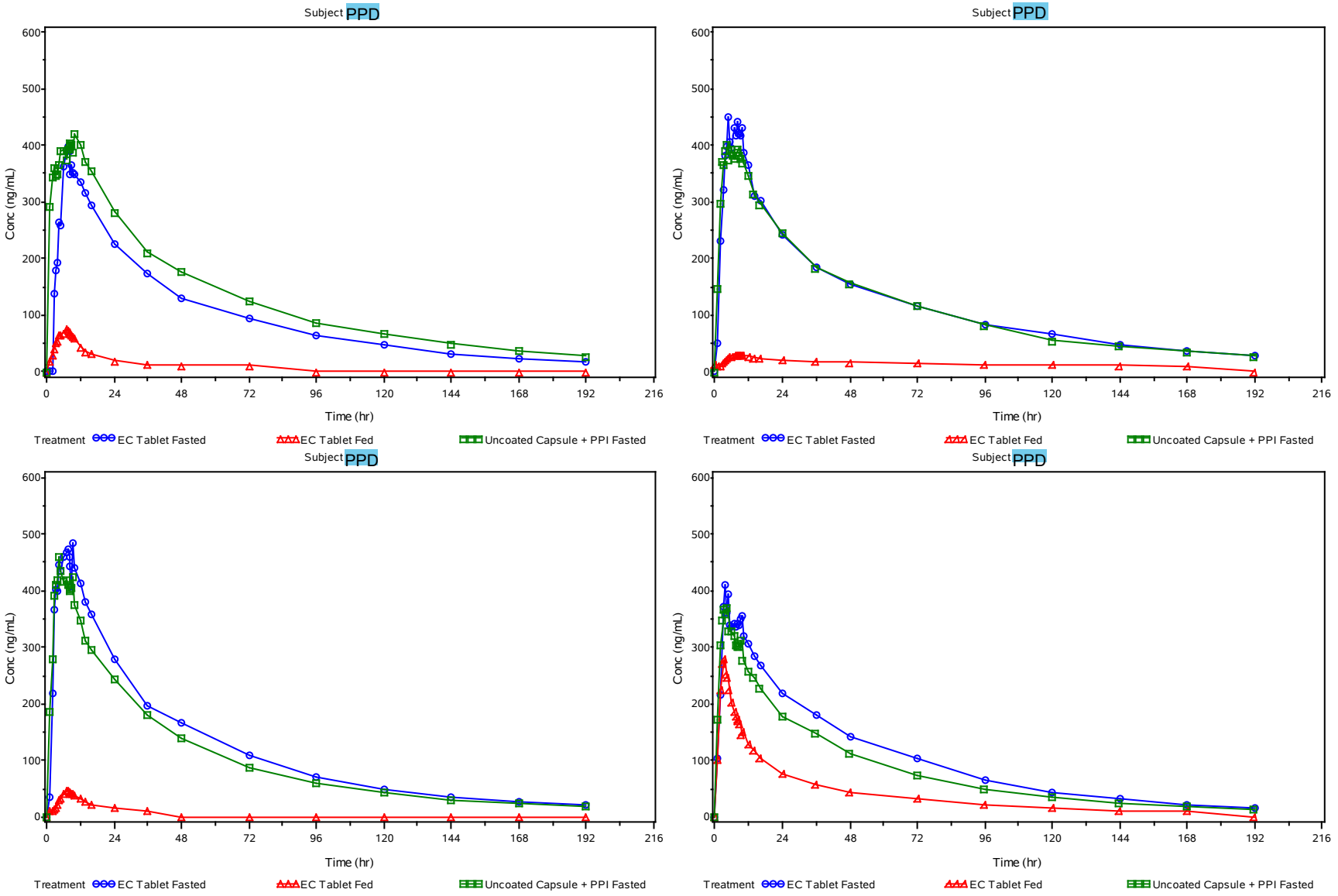
Comparison	Parameter	Geometric Means: Test	Geometric Means: Reference	Geometric Mean Ratio	90% Confidence Interval: Lower Limit	90% Confidence Interval: Upper Limit	Within Subject CV (%)	Power* (%)
B-A	CMAX	146.11	360.88	40.49	31.12	52.68	47.98	67.14
	AUC(0-t)	3,726.71	14,790.84	25.20	17.21	36.89	73.76	77.30
	AUC(inf)	5,071.14	15,997.76	31.70	23.12	43.47	55.30	72.58
A-C	CMAX	360.88	436.61	82.65	63.91	106.90	47.98	66.48
	AUC(0-t)	14,790.84	19,511.14	75.81	52.23	110.02	73.76	76.76
	AUC(inf)	15,997.76	18,353.45	87.16	64.59	117.63	55.30	71.10

Data were natural log-transformed before analysis.
*Power to detect a 20% difference at alpha = 0.05.
tment A - EC Tablet Fasted; Treatment B - EC Tablet Fed; Treatment C - Uncoated Capsule + PPI Fasted
Subject PPD Period 2, EC Tablet Fed, had a C(0) >= LOQ and >= 5% of Cmax and is excluded from the statistical analyses.

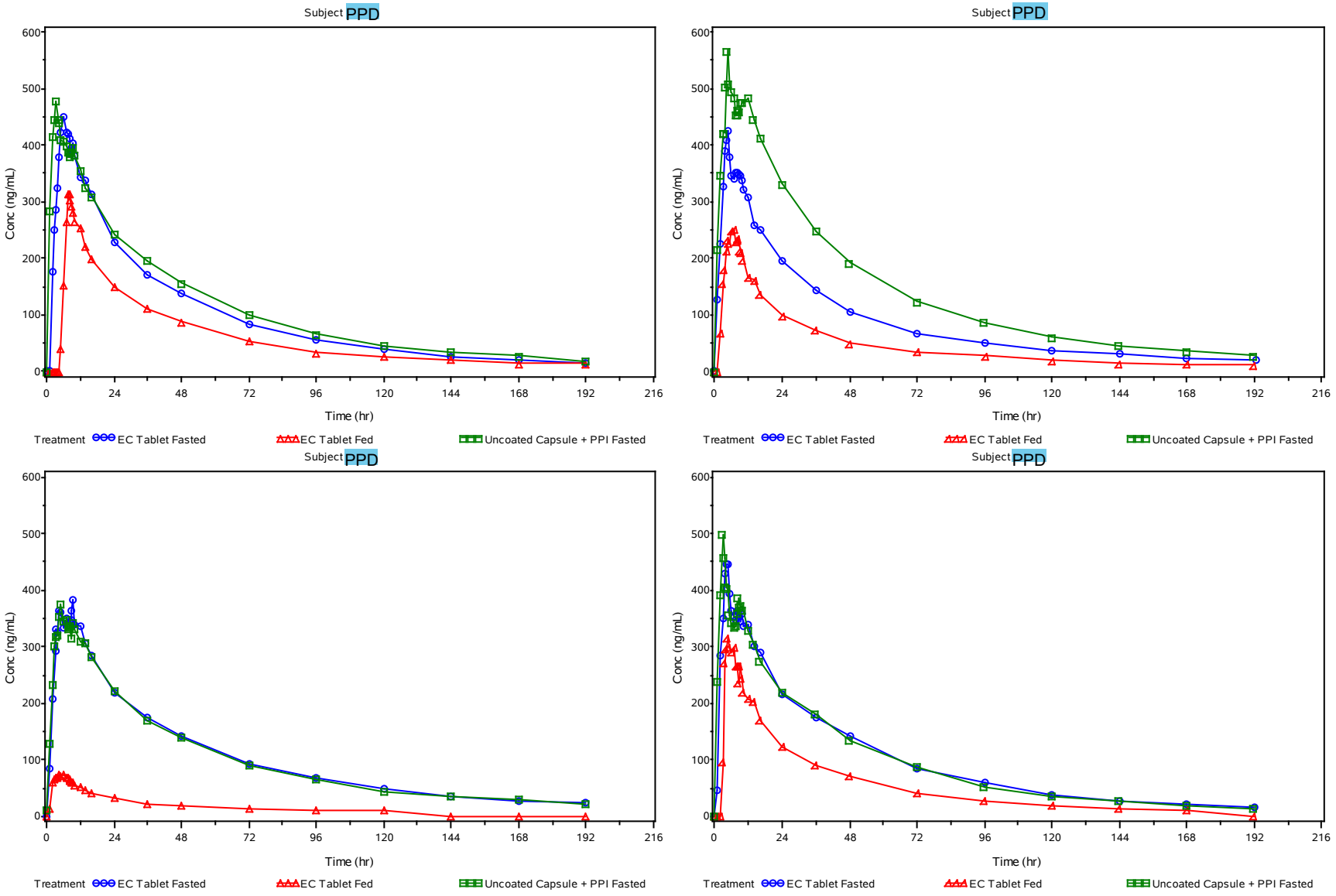
Appendix IX — Individual Subject Total Mo Concentration vs. Time Graphs — Linear Axes



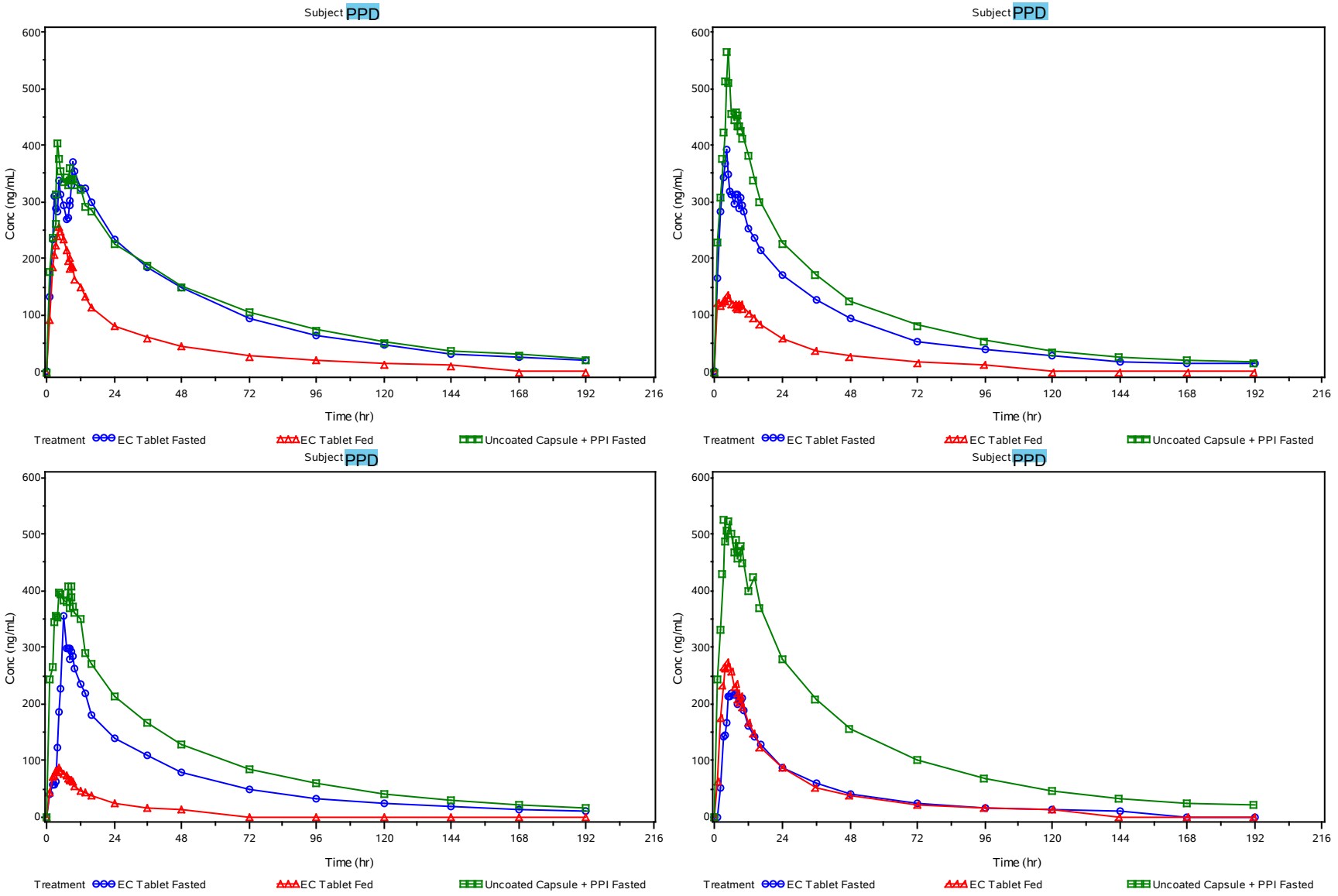
Appendix IX — Individual Subject Total Mo Concentration vs. Time Graphs — Linear Axes



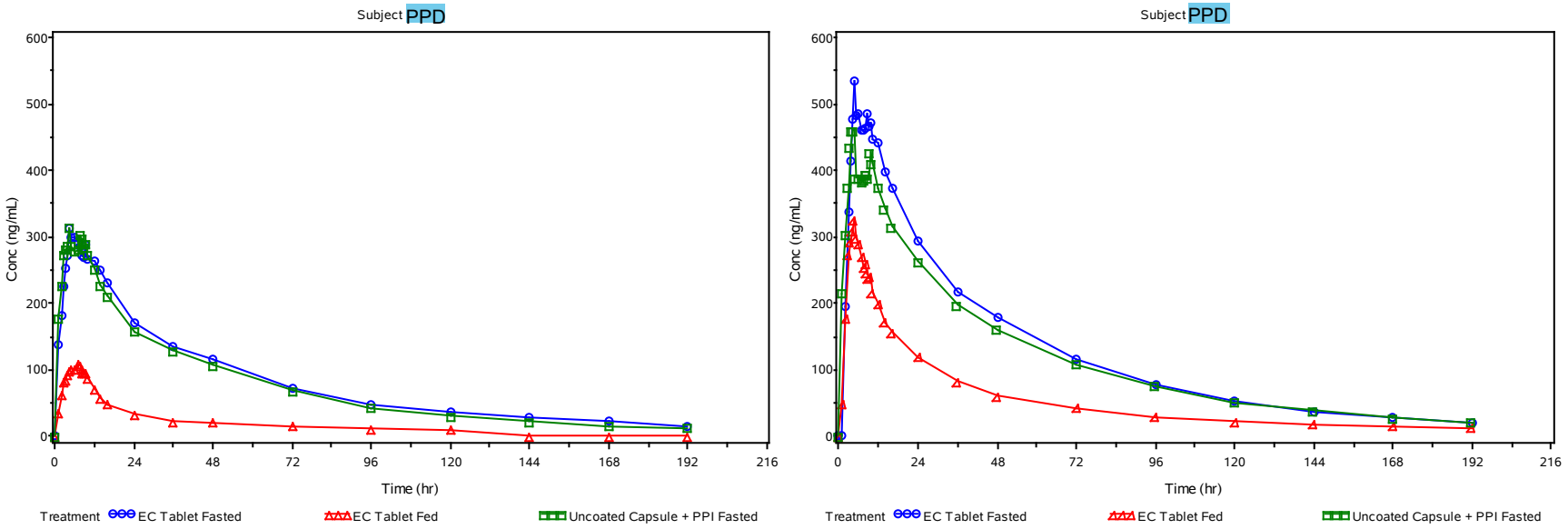
Appendix IX — Individual Subject Total Mo Concentration vs. Time Graphs — Linear Axes



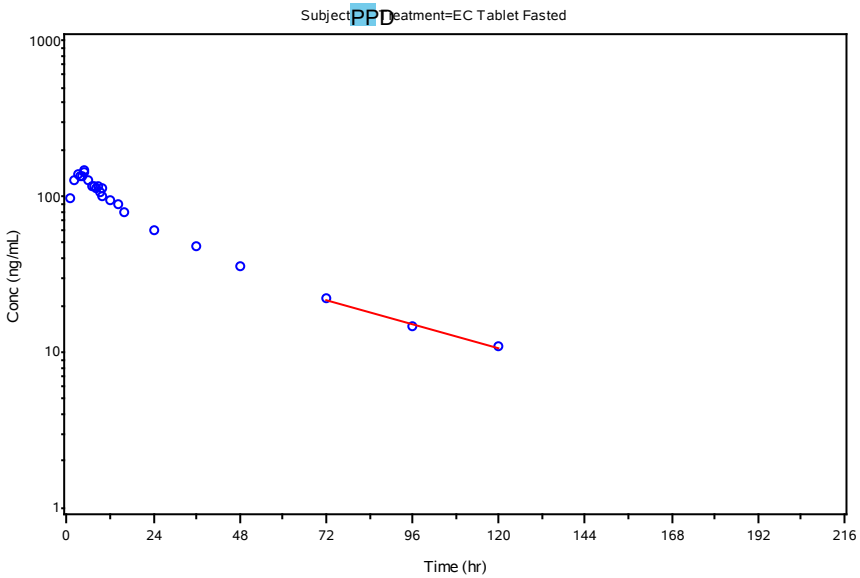
Appendix IX — Individual Subject Total Mo Concentration vs. Time Graphs — Linear Axes

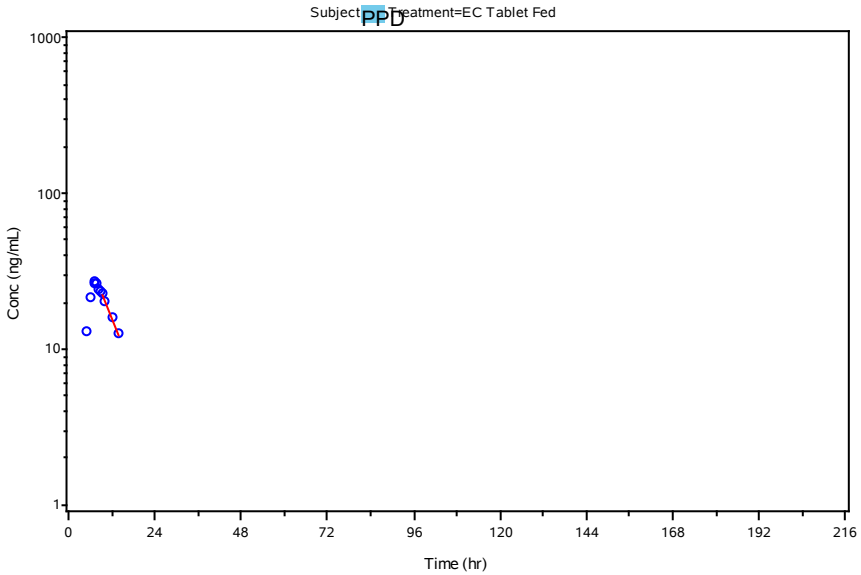


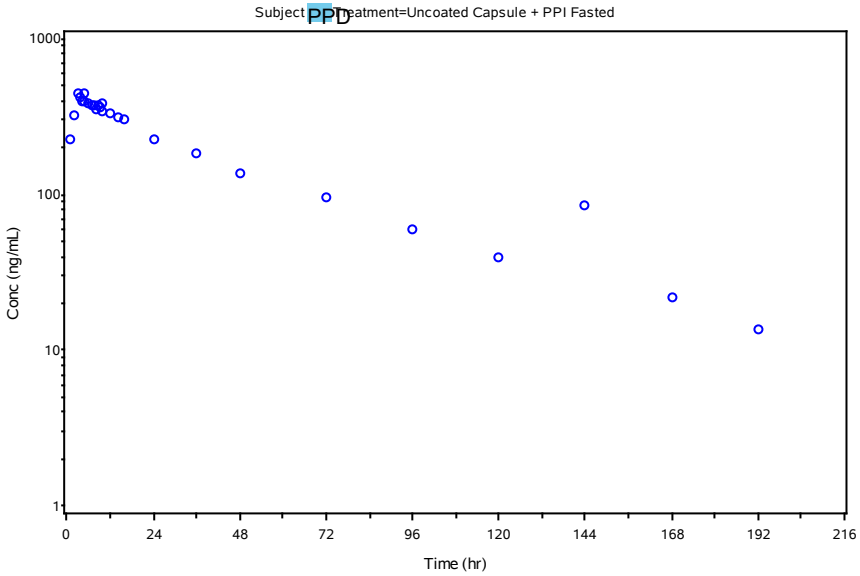
Appendix IX — Individual Subject Total Mo Concentration vs. Time Graphs — Linear Axes



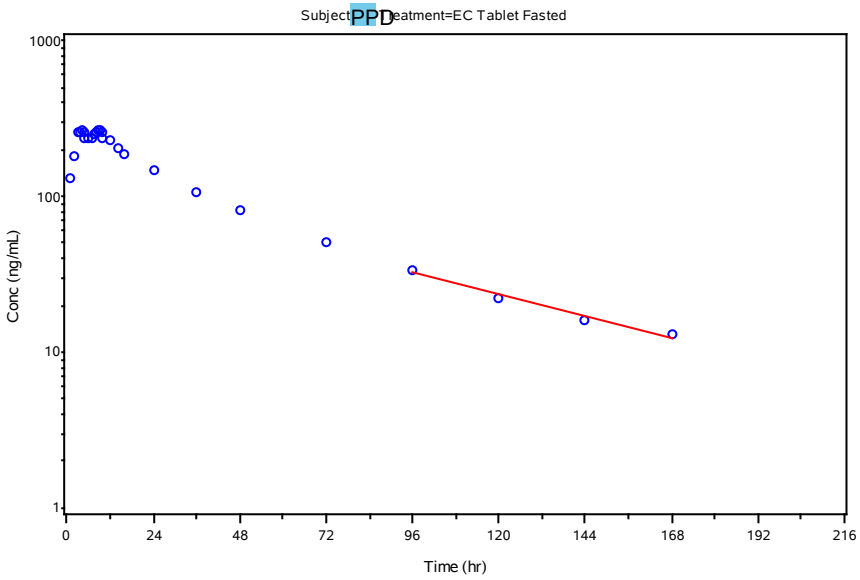
Appendix X — Individual Subject Total Mo Concentration vs. Time Graphs — Semi-Logarithmic Axes

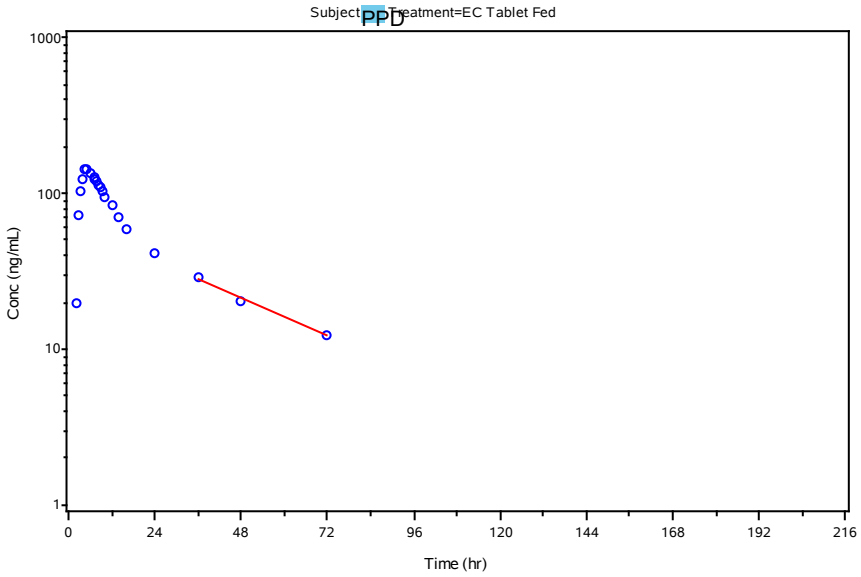


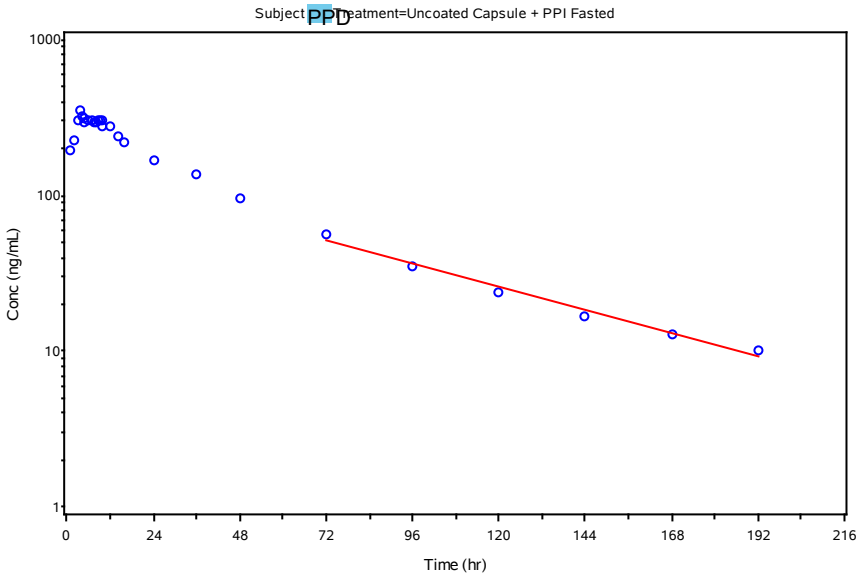




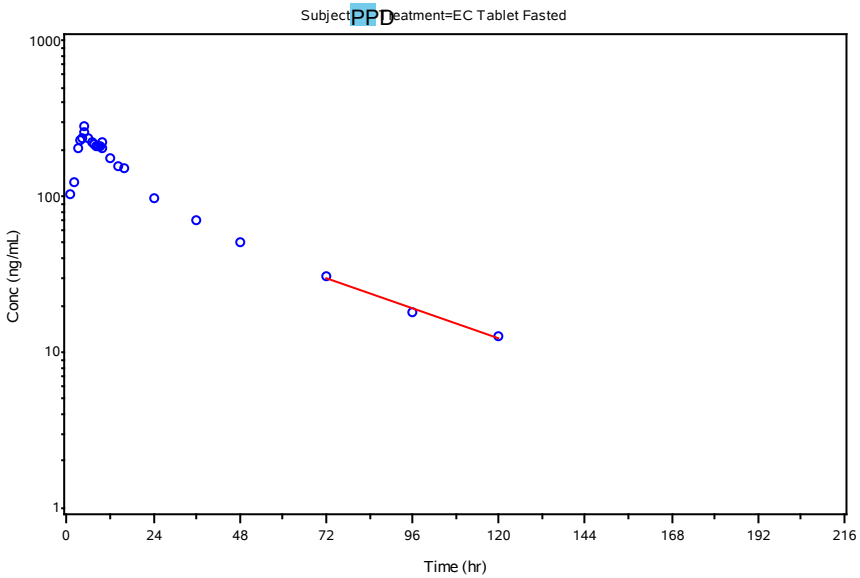
Appendix X — Individual Subject Total Mo Concentration vs. Time Graphs — Semi-Logarithmic Axes

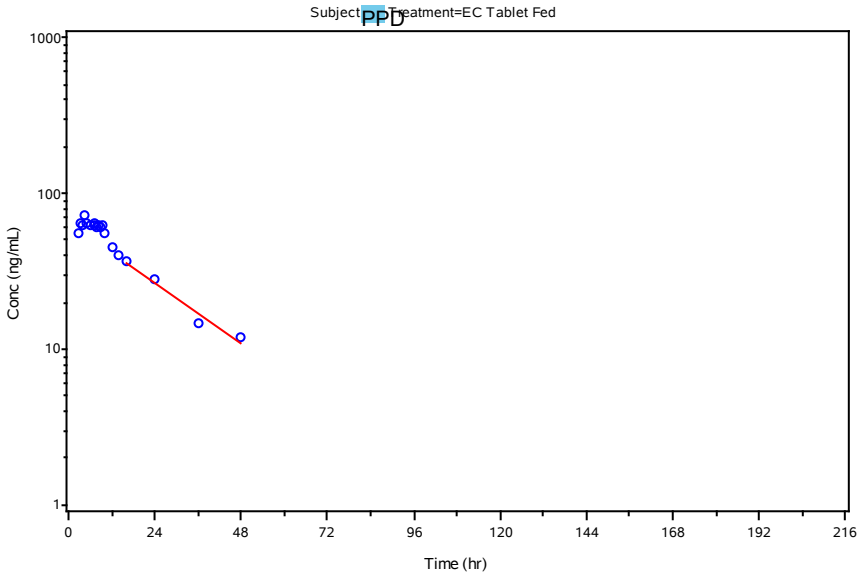


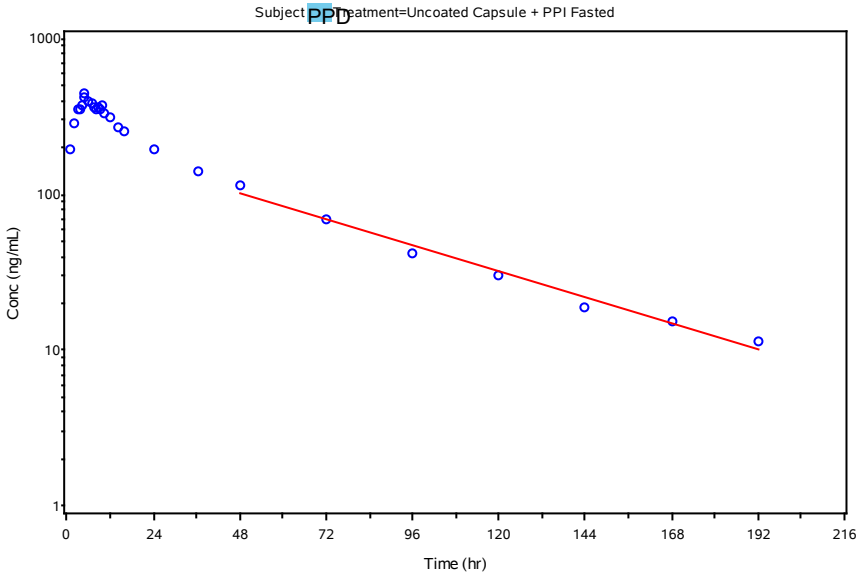




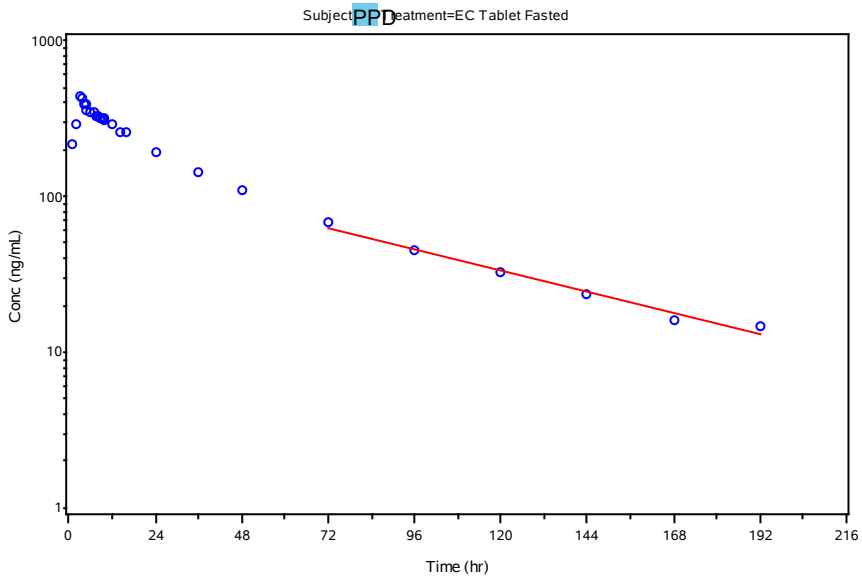
Appendix X — Individual Subject Total Mo Concentration vs. Time Graphs — Semi-Logarithmic Axes

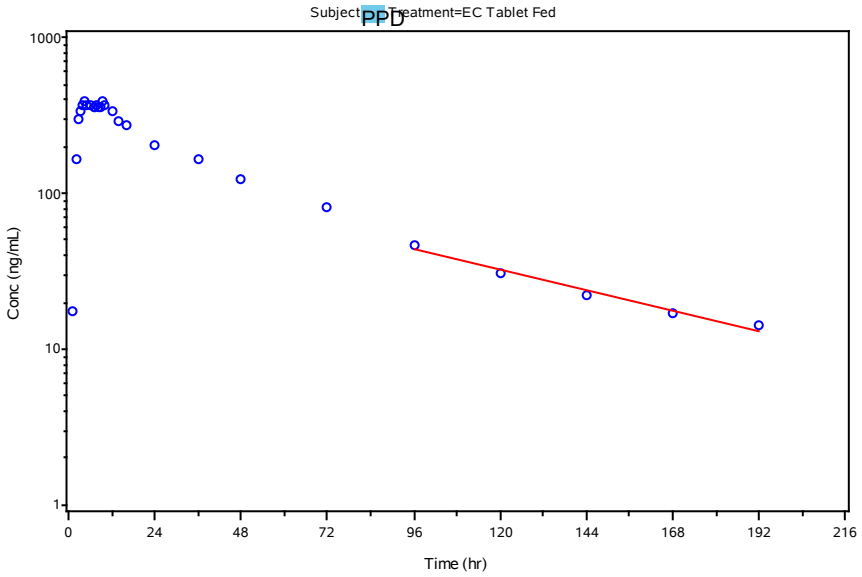


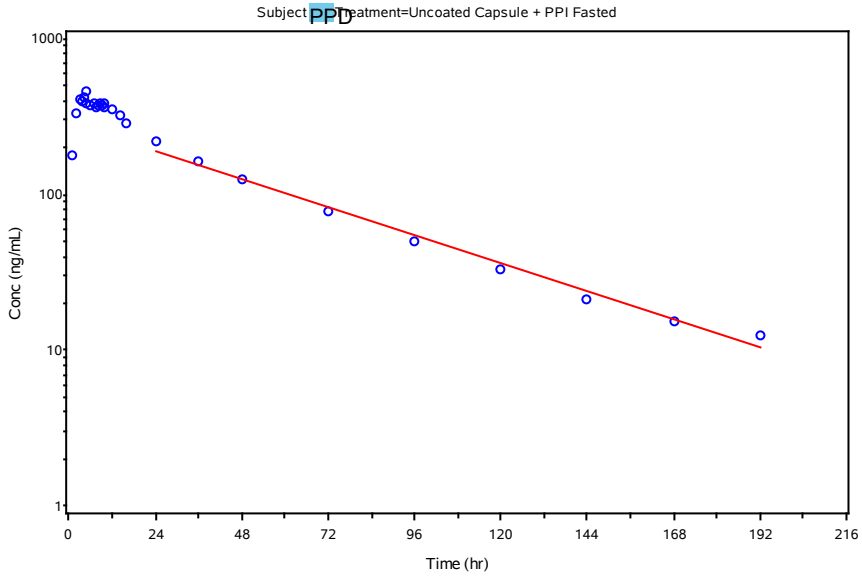




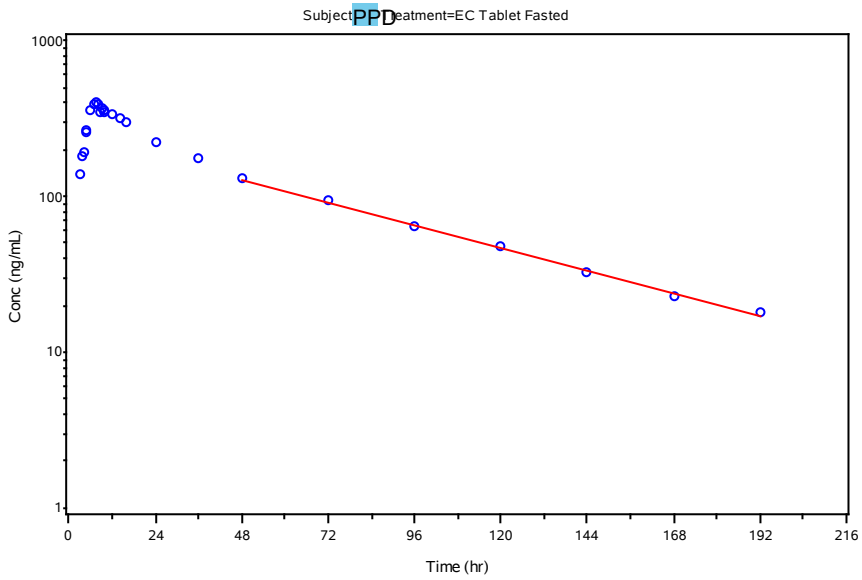
Appendix X — Individual Subject Total Mo Concentration vs. Time Graphs — Semi-Logarithmic Axes

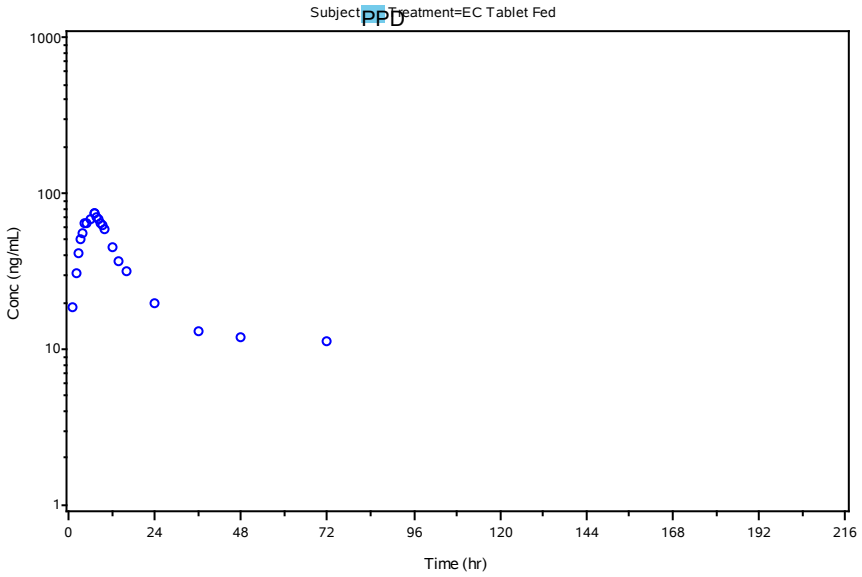


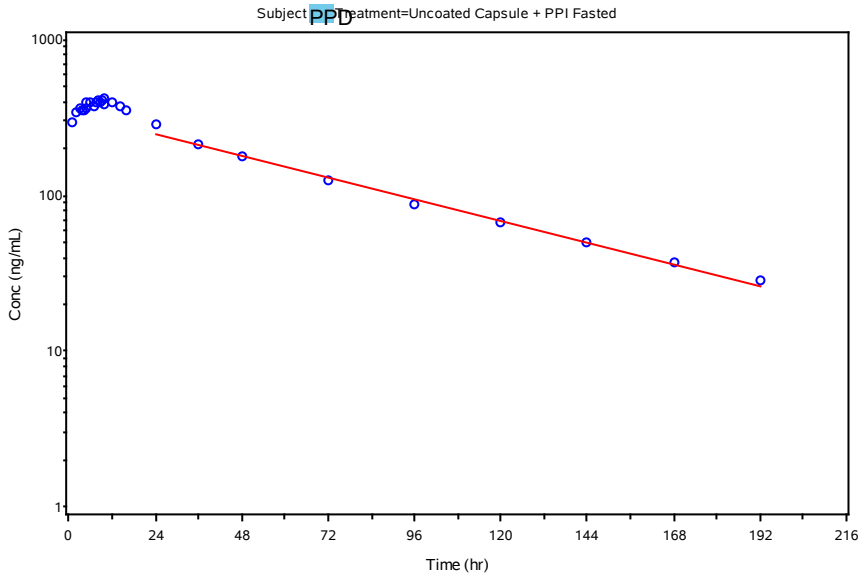




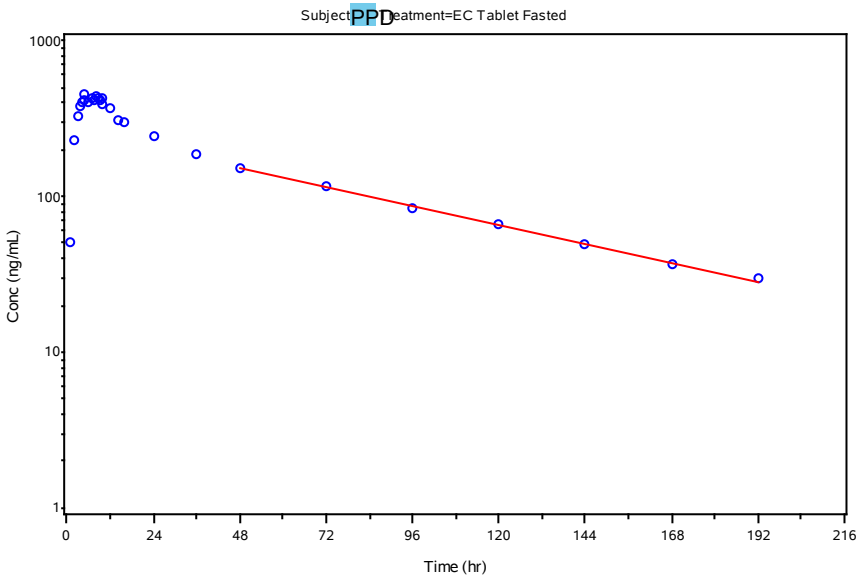
Appendix X — Individual Subject Total Mo Concentration vs. Time Graphs — Semi-Logarithmic Axes

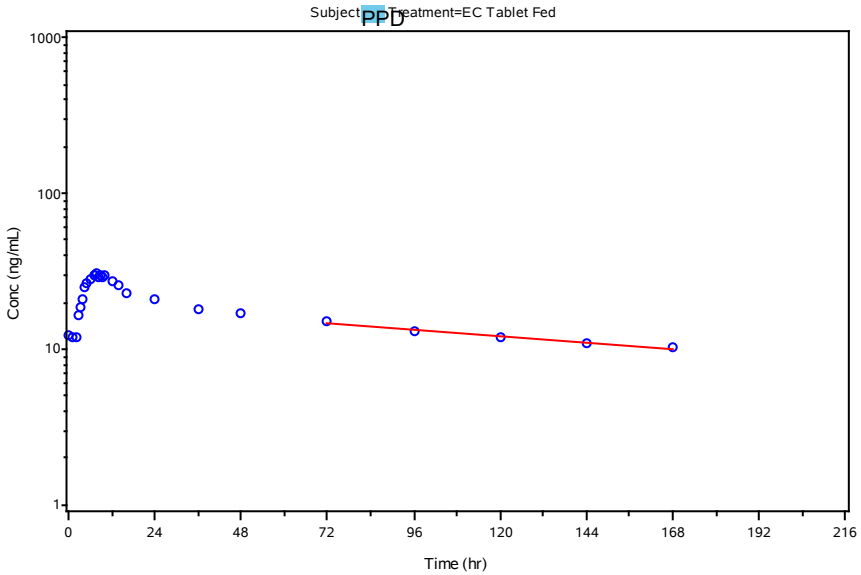


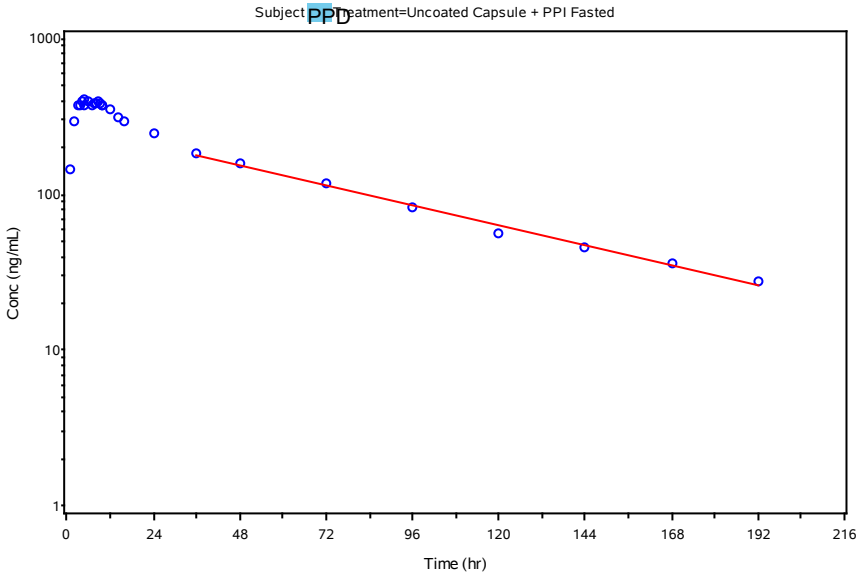




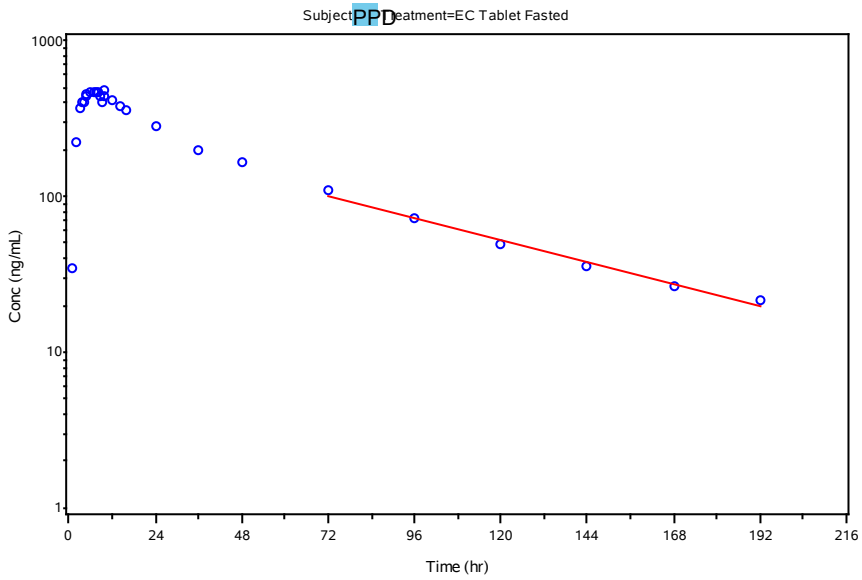
Appendix X — Individual Subject Total Mo Concentration vs. Time Graphs — Semi-Logarithmic Axes

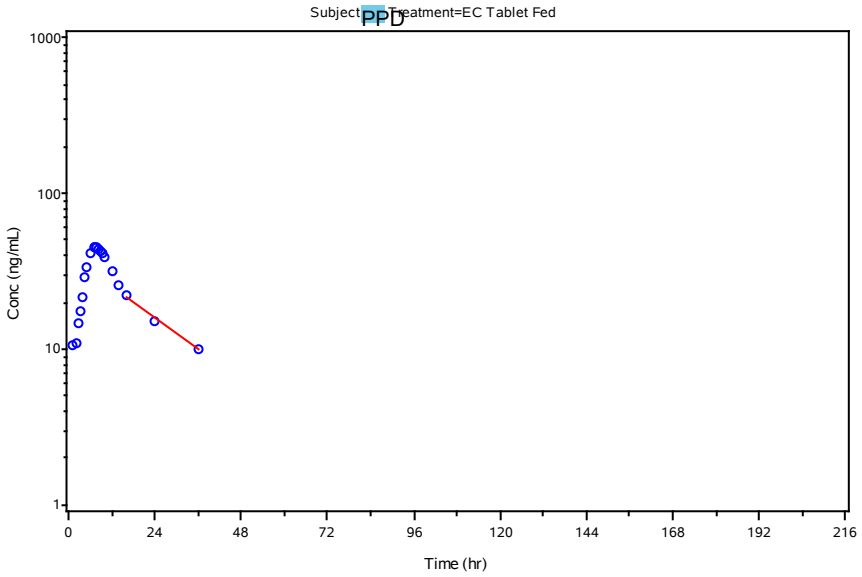


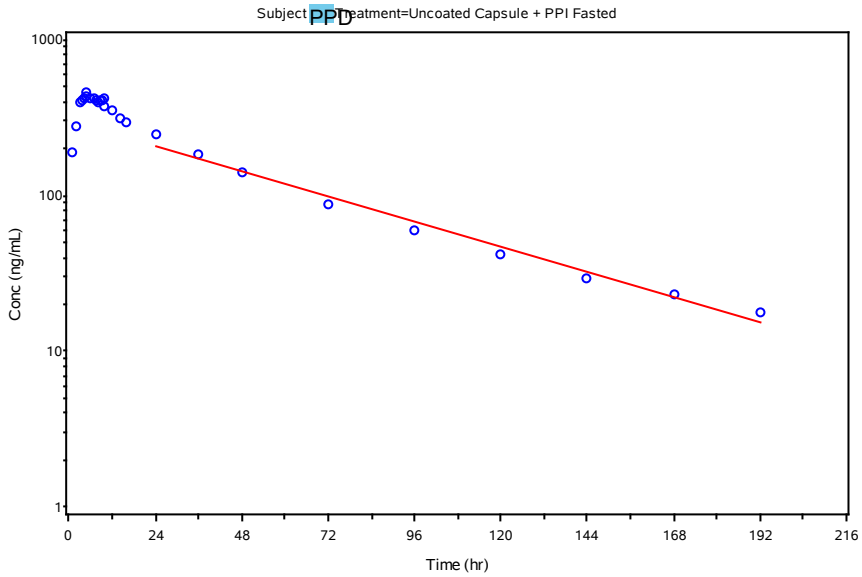




Appendix X — Individual Subject Total Mo Concentration vs. Time Graphs — Semi-Logarithmic Axes







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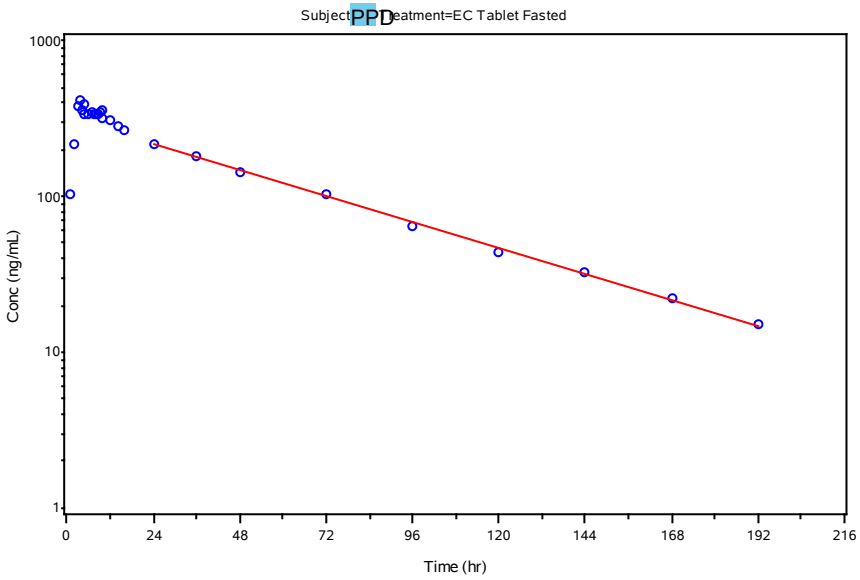

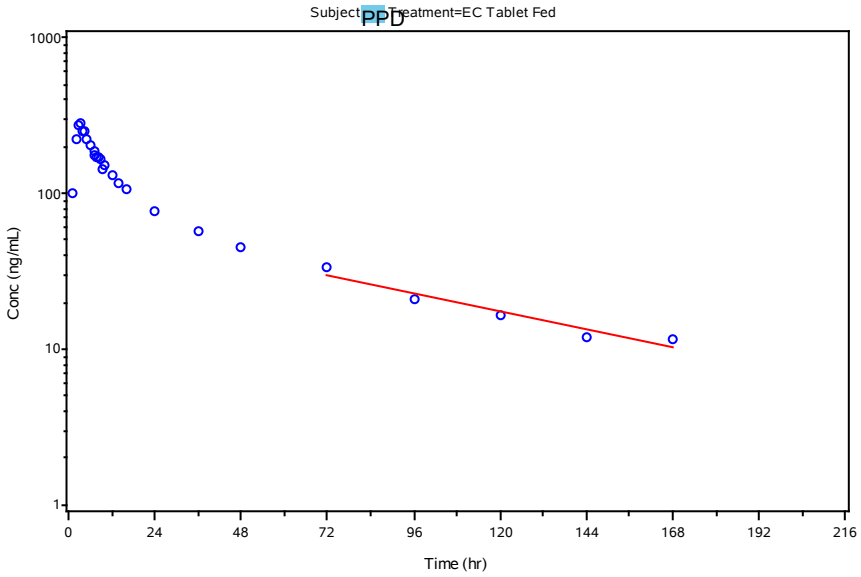

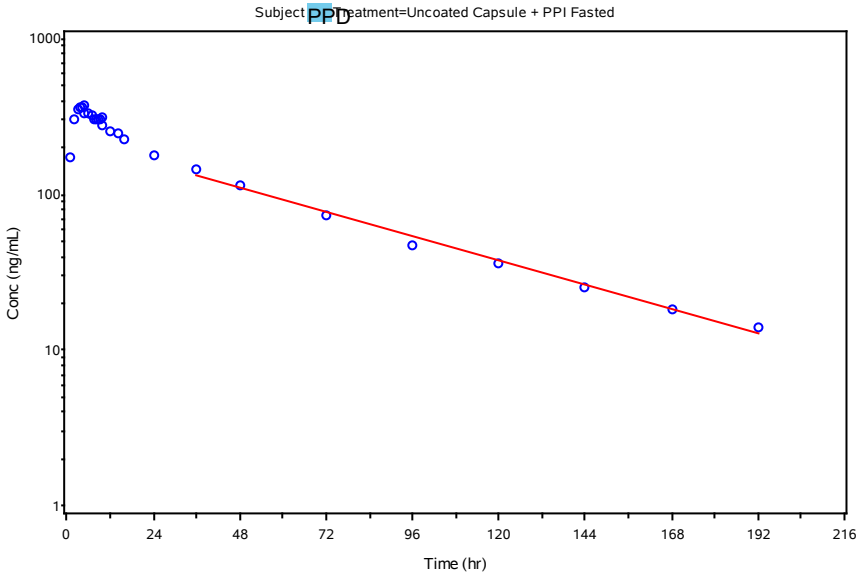

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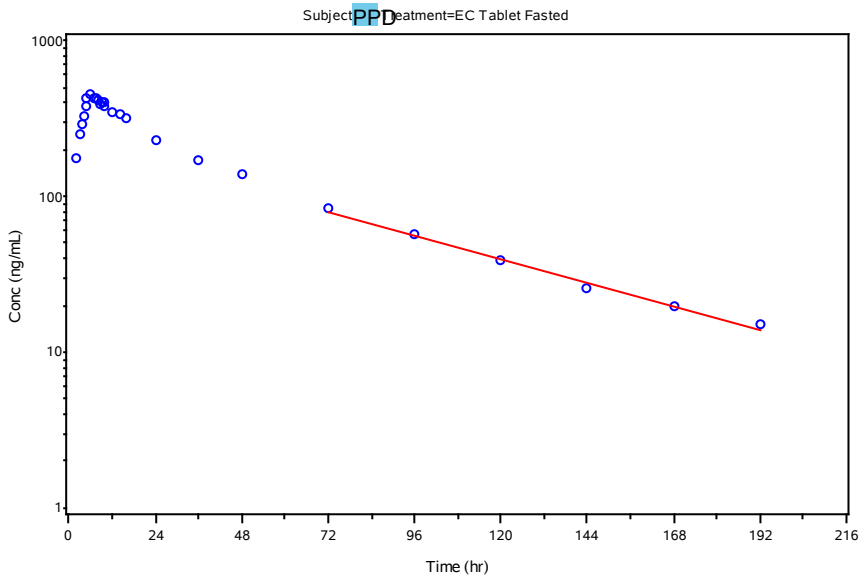

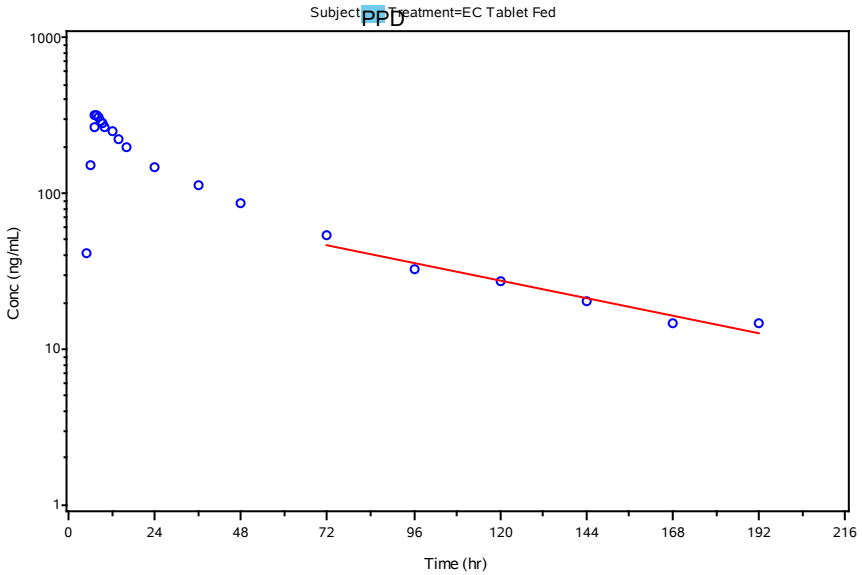

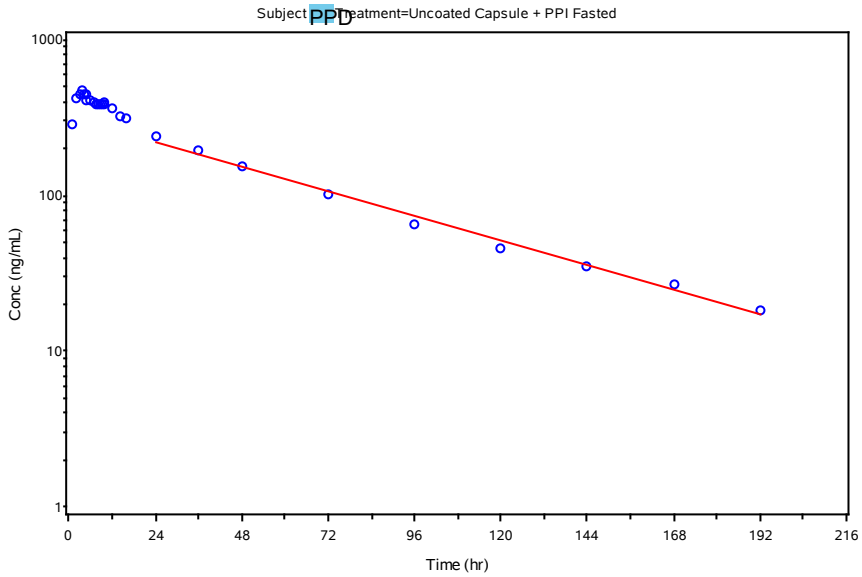

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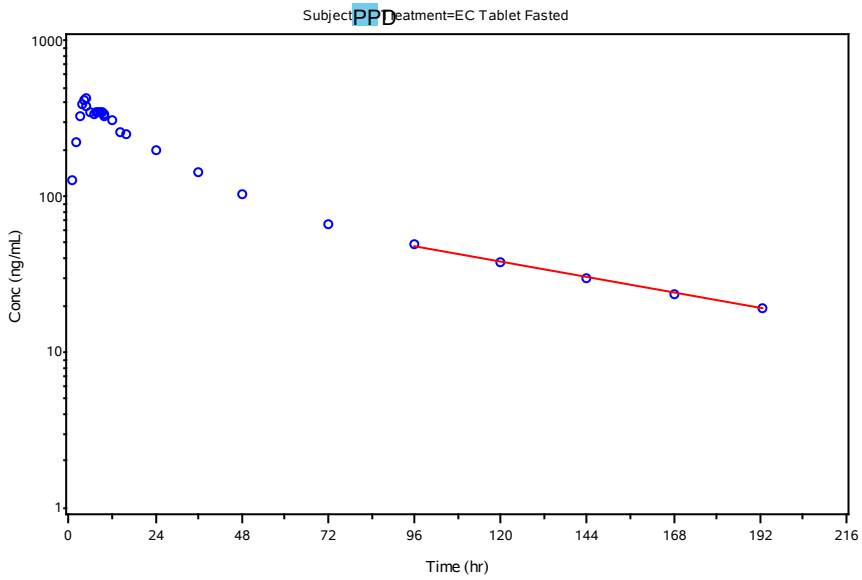

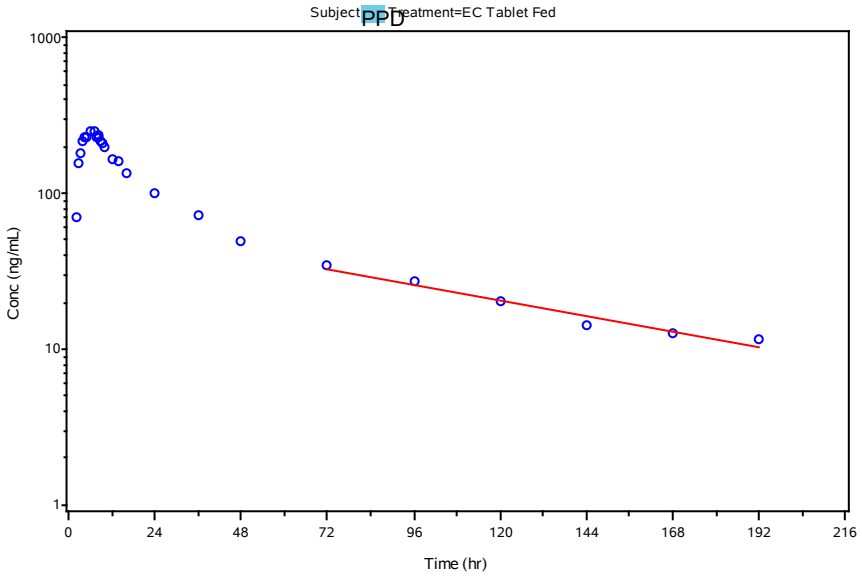

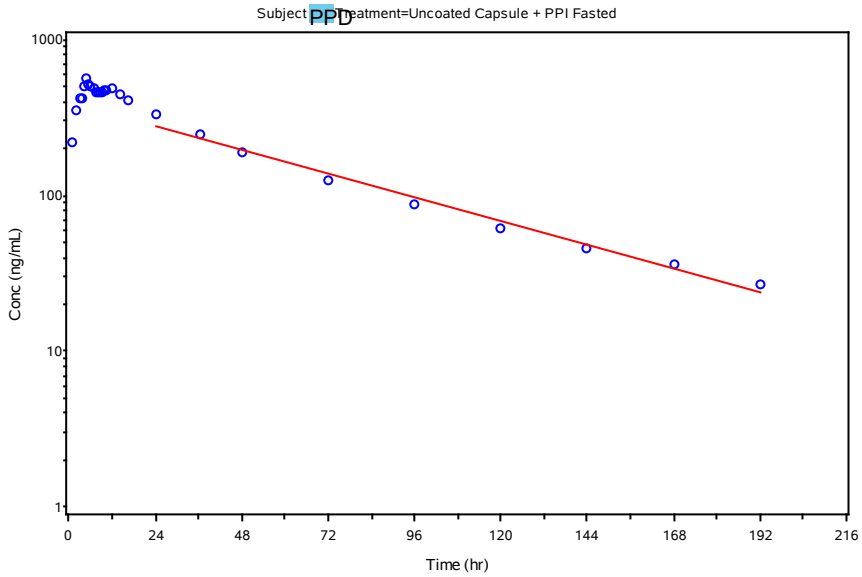

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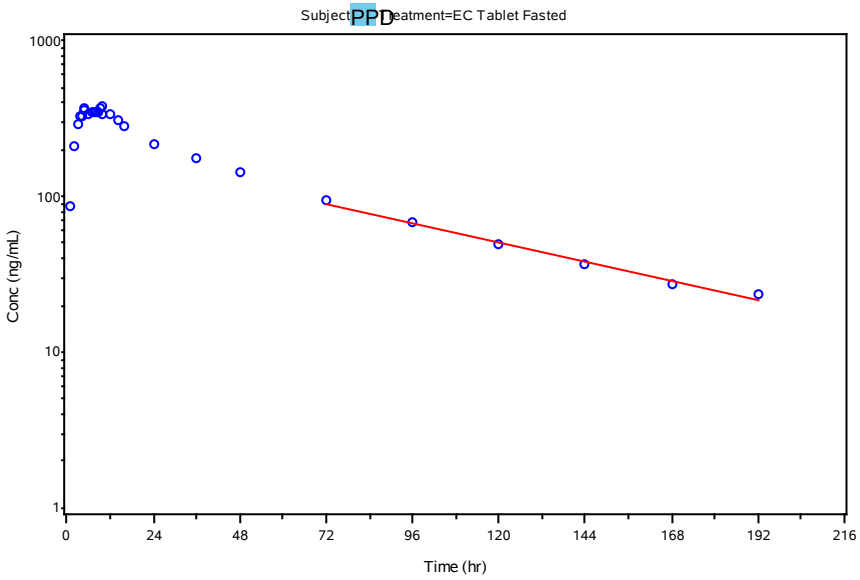

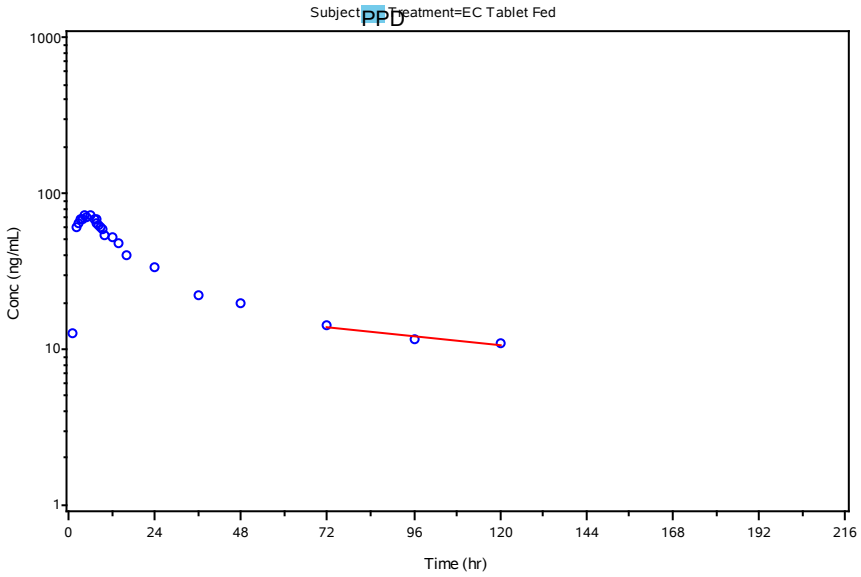

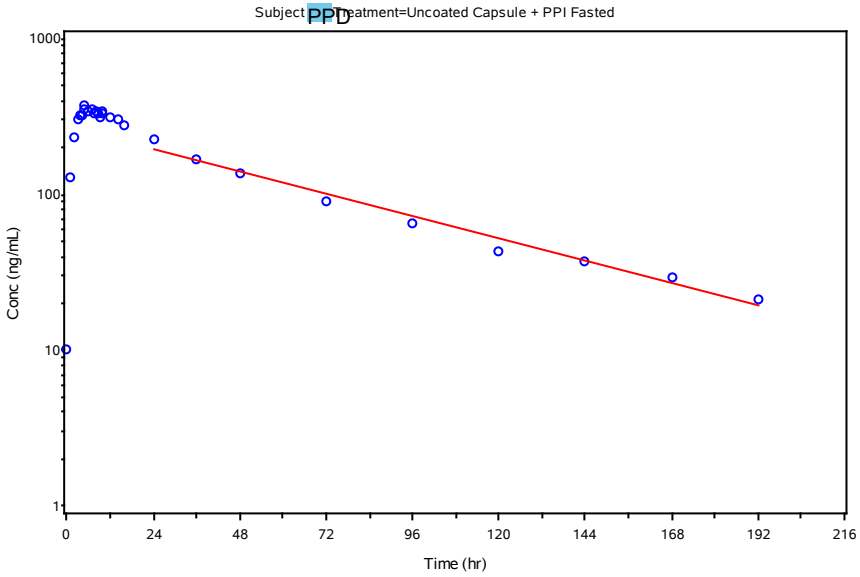

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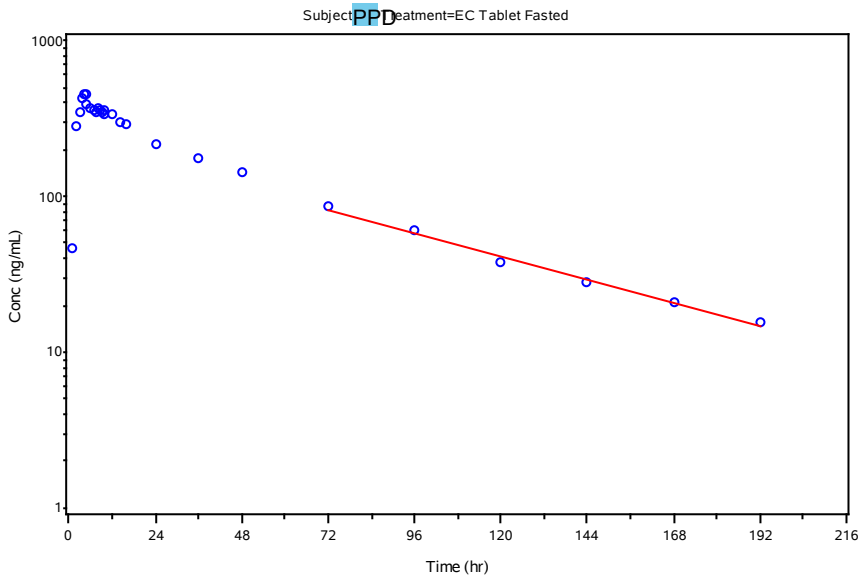

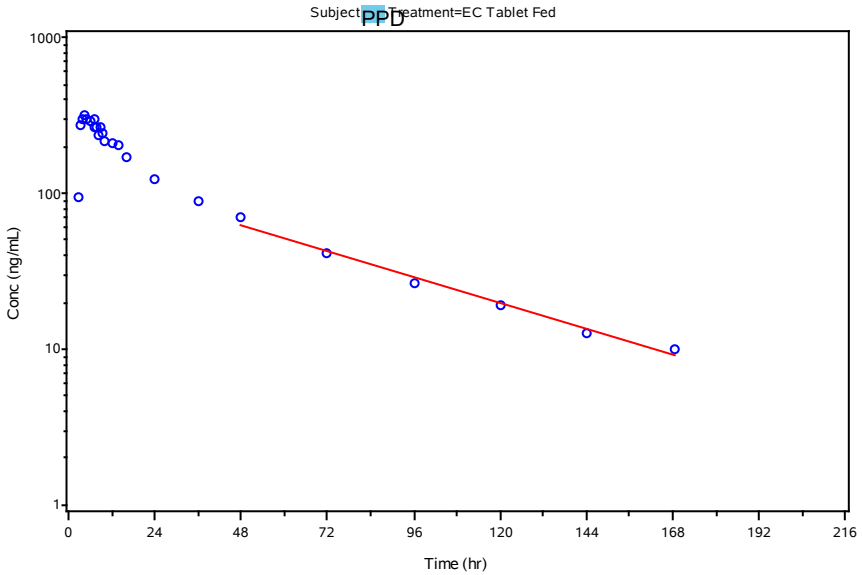

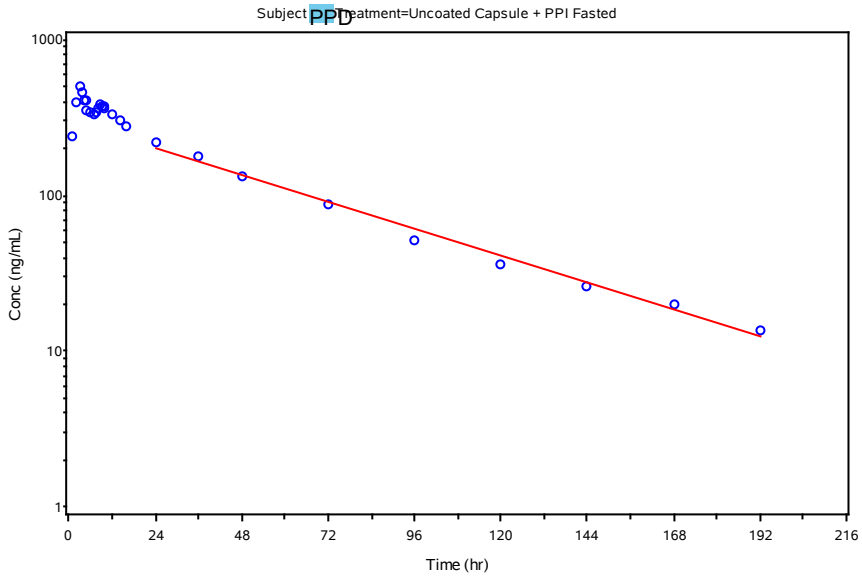

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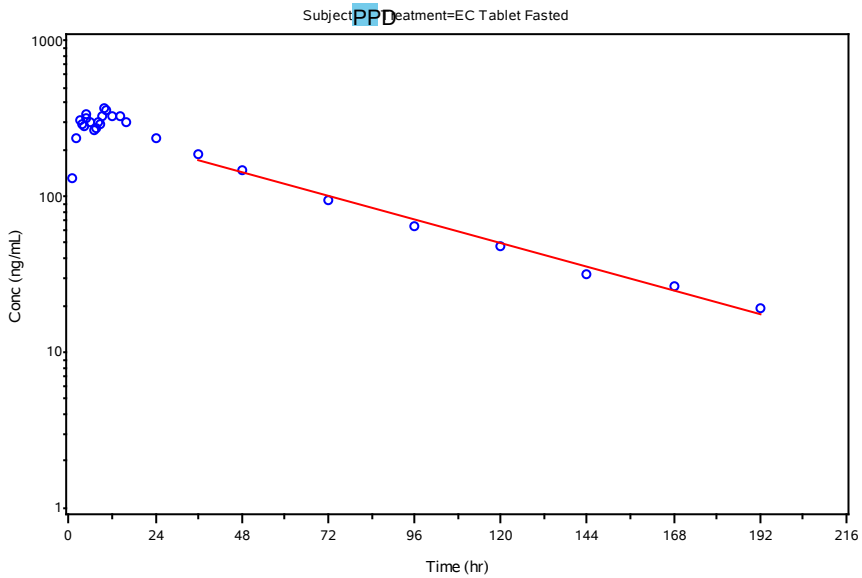

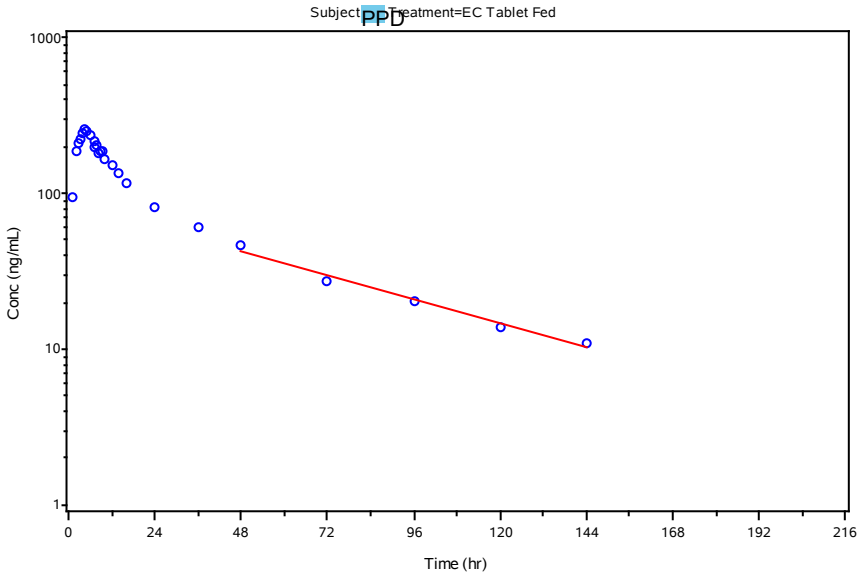

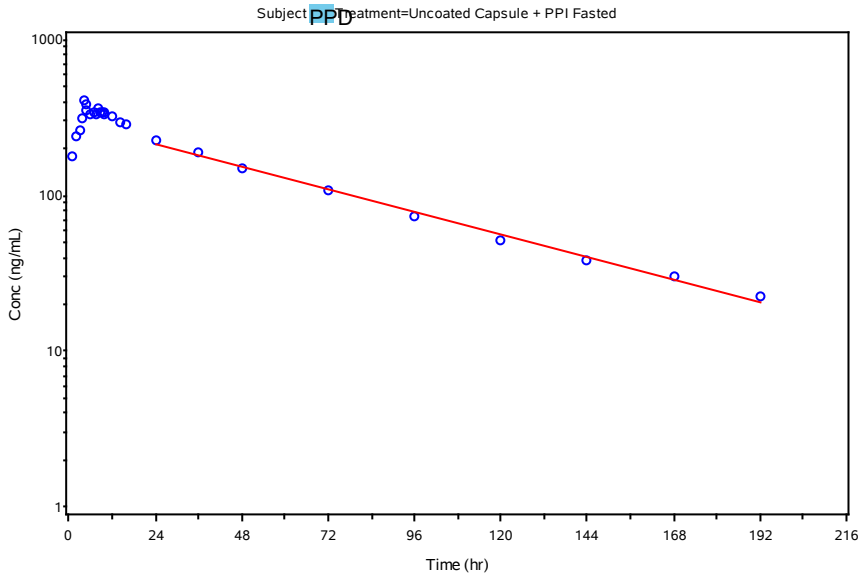

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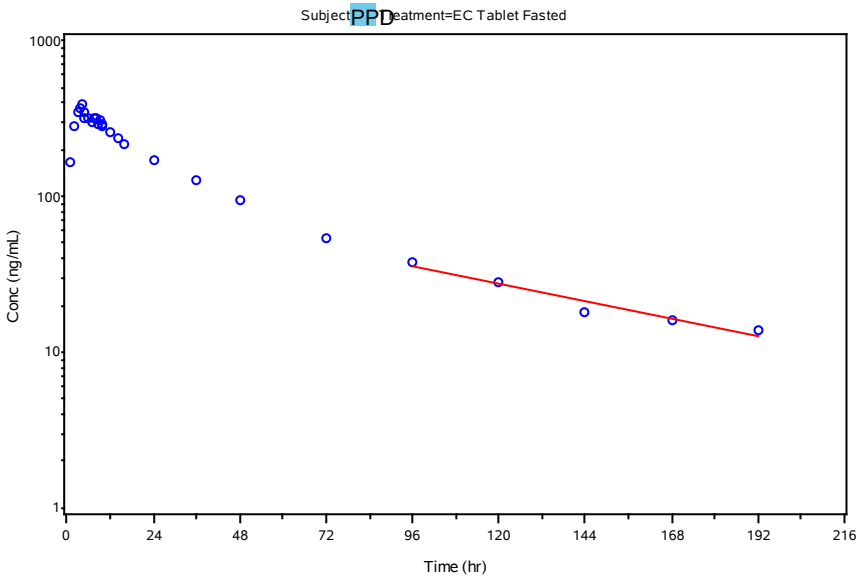

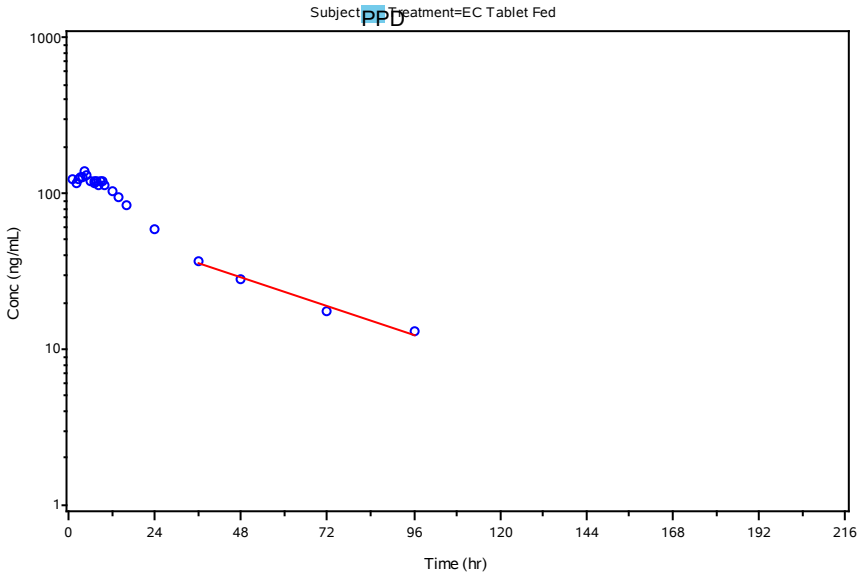

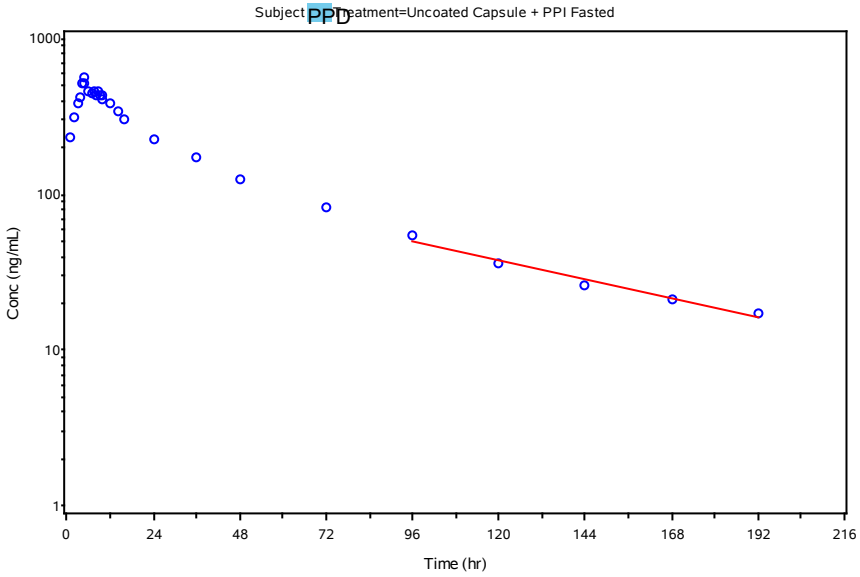

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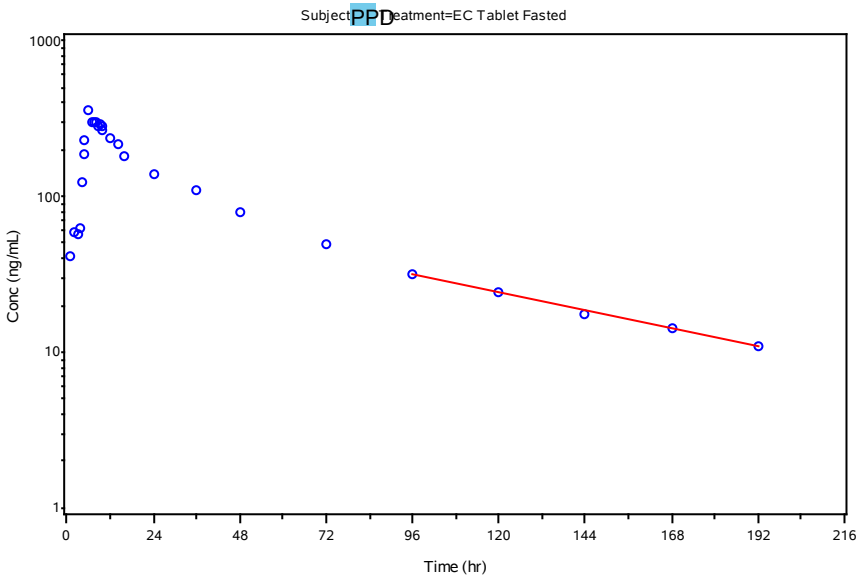

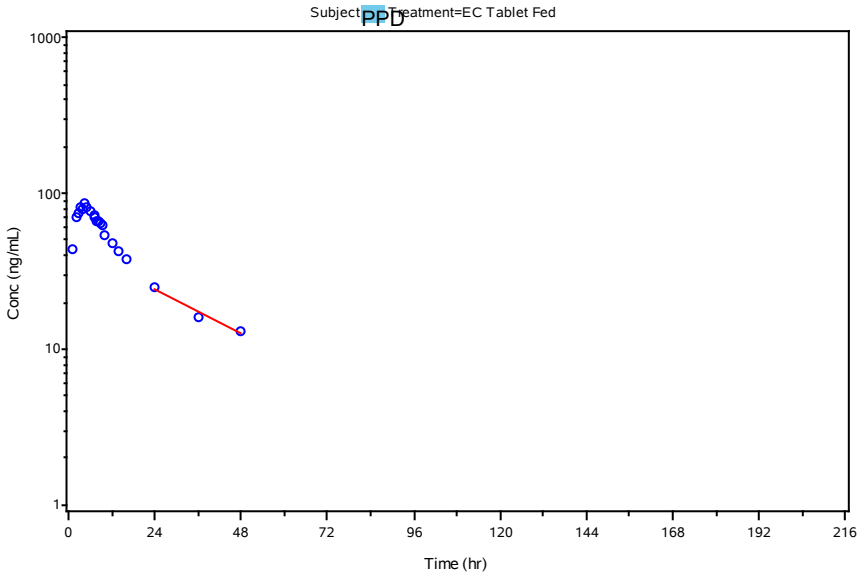

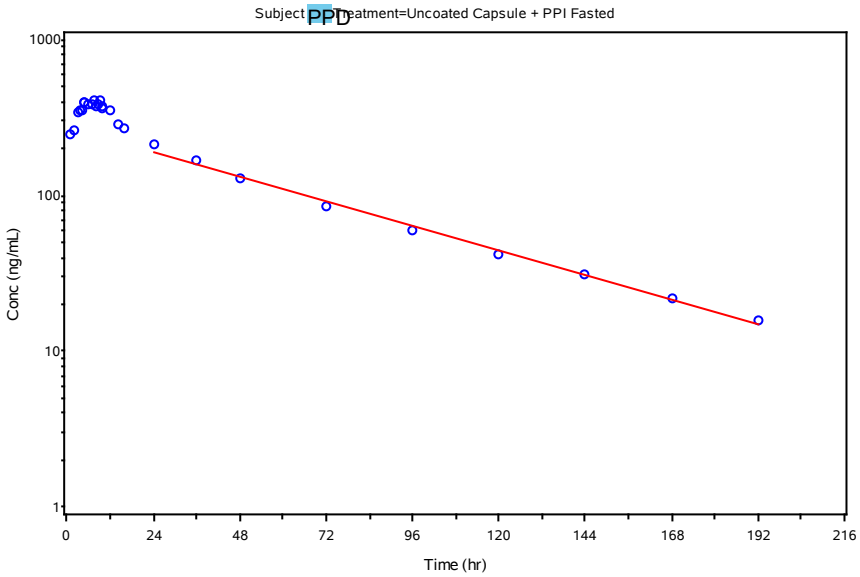

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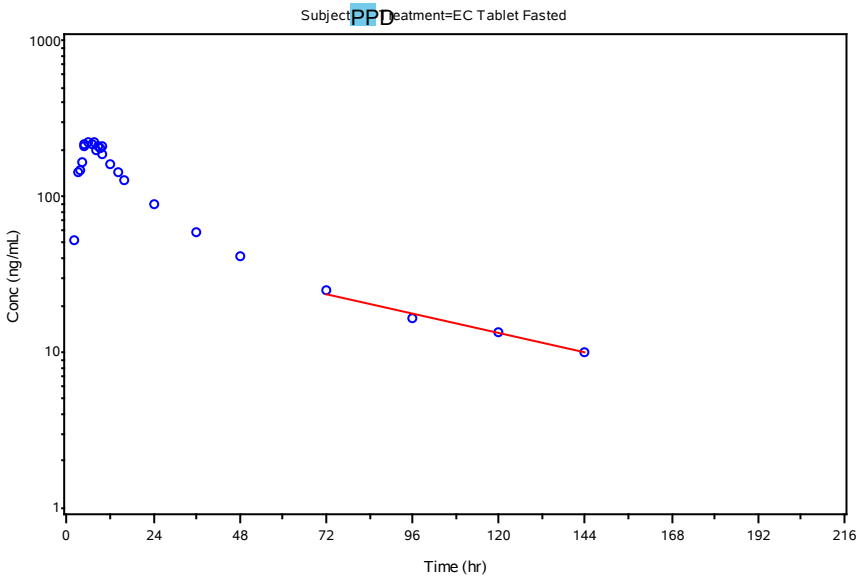

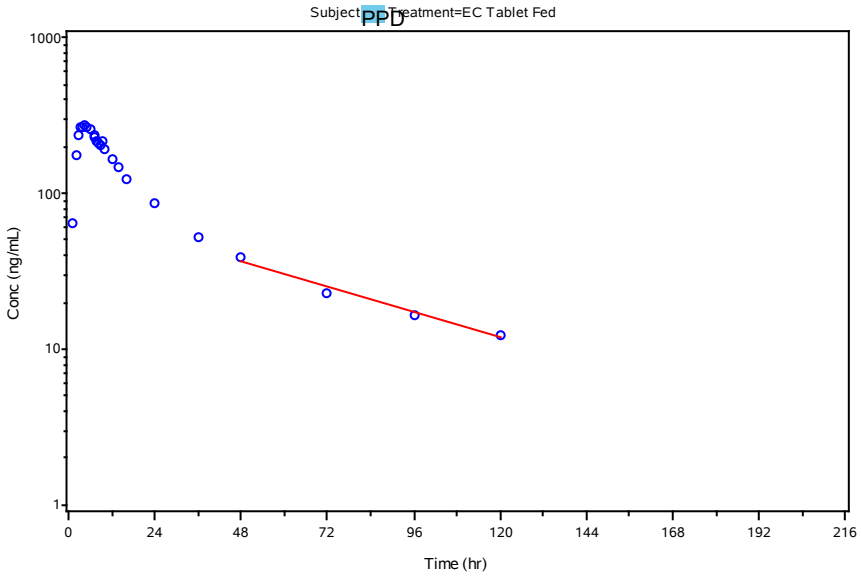

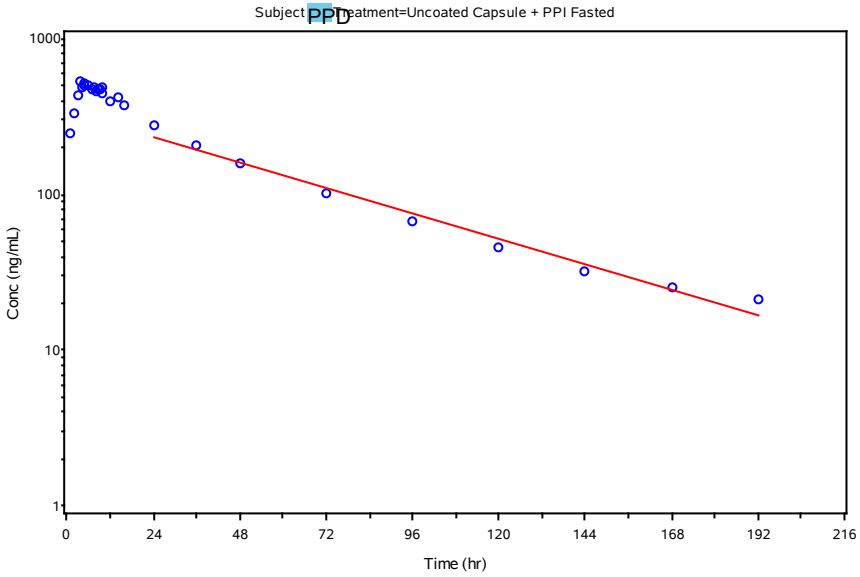

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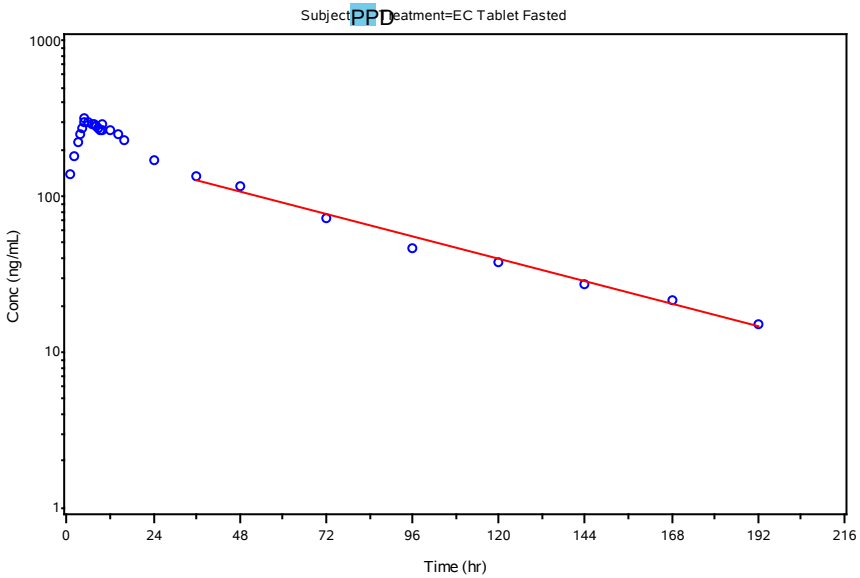

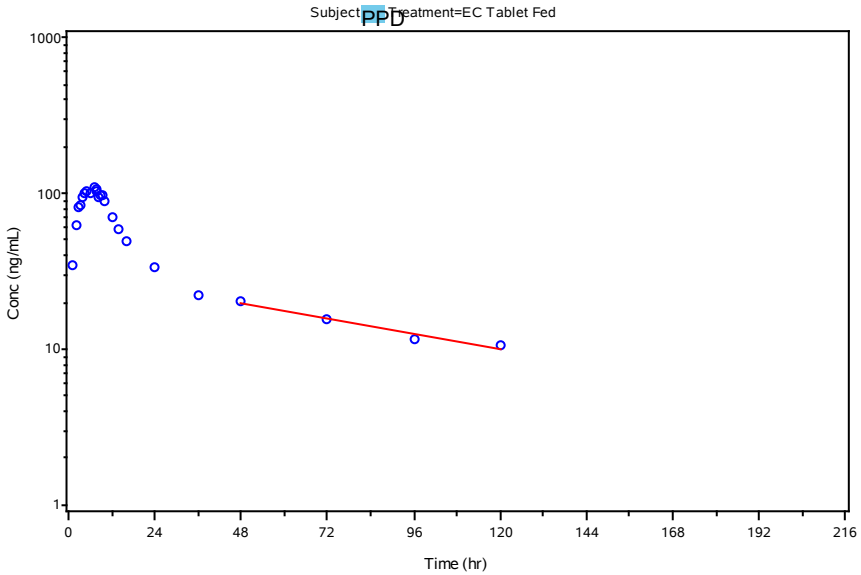

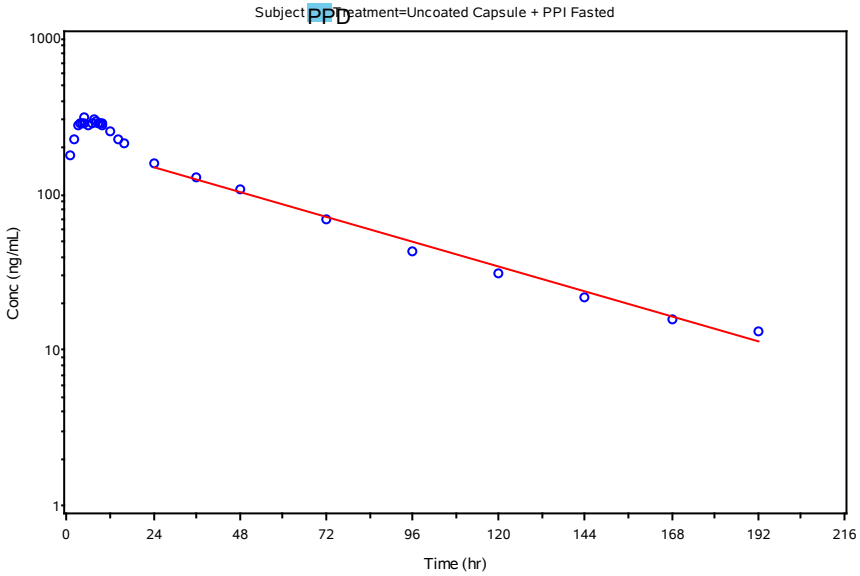

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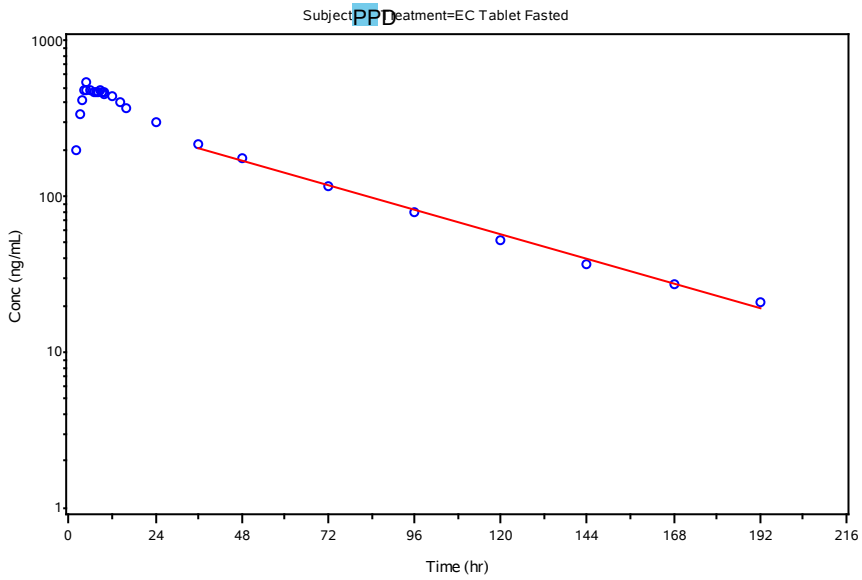

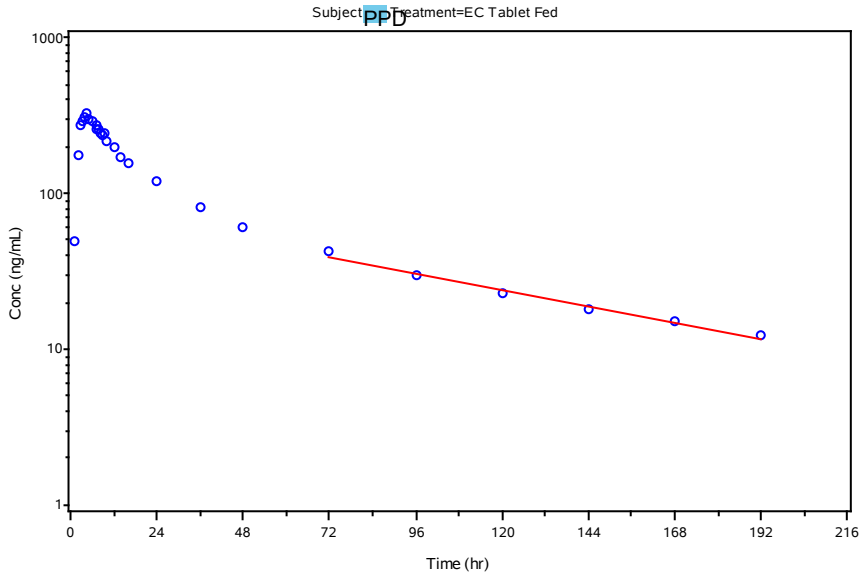

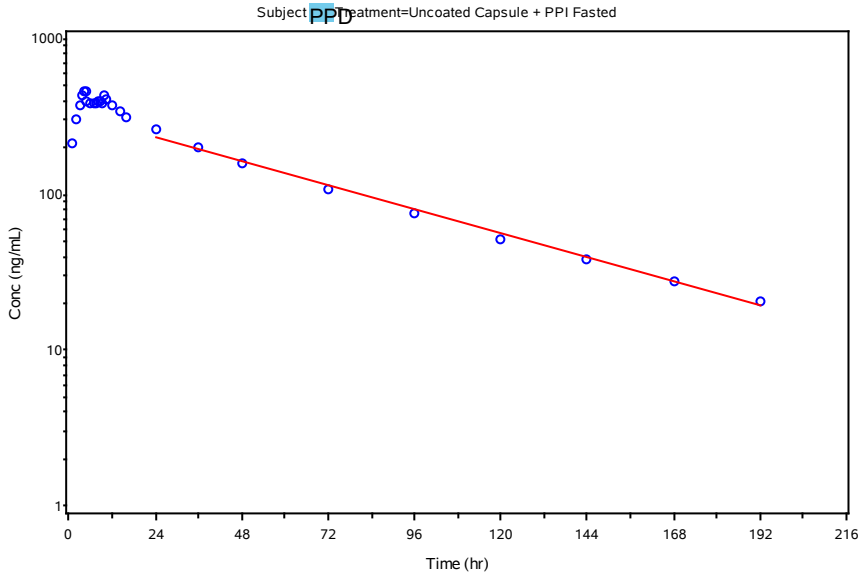

16.1.9.2 Statistical Methods

16.1.9.2.1 Statistical Analysis Plan

Statistical Analysis Plan

A Phase 1, Single-Center, Randomized, 3-Period Crossover Study in Healthy Volunteers to Evaluate the Absorption of WTX101 After Single Dose Administration of an Enteric Coated Formulation with and without food and a Non-Coated Formulation Coadministered with a Proton Pump Inhibitor without Food

Protocol No. WTX101-102
Celerion Project CA13895

Final Version 1.0
Date: 12 May 2014

Compound Name: WTX101

Final Protocol Date: 25 February 2014

Sponsor:
Wilson Therapeutics USA, Inc.
P.O. Box 17757
Urbana, Illinois 61803 - USA

Wilson Therapeutics, AB
Västra Trädgårdsgatan 15
11453 Stockholm, Sweden

Sponsor Representative:
PPD
11 Ridgefield Road
Winchester, Massachusetts, 01890, USA

Celerion
621 Rose Street
Lincoln, NE 68502

Statistical Analysis Plan Signature Page

Sponsor: Wilson Therapeutics USA, Inc.
P.O. Box 17757
Urbana, Illinois 61803 - USA

Wilson Therapeutics, AB
Västra Trädgårdsgatan 15
11453 Stockholm, Sweden

Compound Name: WTX101

Protocol: WTX101-102

Study Title: A Phase 1, Single-Center, Randomized, 3-Period Crossover Study in Healthy Volunteers to Evaluate the Absorption of WTX101 After Single Dose Administration of an Enteric Coated Formulation with and without food and a Non-Coated Formulation Coadministered with a Proton Pump Inhibitor without Food

Issue Date: 12 May 2014

Signature: PPD _____ Date: 13 MAY 2014

Celerion
621 Rose Street
PPD NE 68502

PPD

Signature: _____ Date: MAY 12 2014

PPD

11 Ridgefield Road
Winchester
Massachusetts, 01890

Table of Contents

1. INTRODUCTION

The following analysis plan provides the framework for the summarization of the data from this study. The analysis plan may change due to unforeseen circumstances. Any changes made after the locking of the database will be documented in the clinical study report. Please note that the header for this page will be the one used for the main body of the report.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

The primary objectives are:

- The effect of dosing with an Enteric coated (EC) tablet versus dosing with the current non-coated capsule administered with a proton pump inhibitor (PPI; omeprazole) under fasting conditions on the absorption of WTX101.
- The effect of dosing an EC tablet with and without food on the absorption of WTX101
- The safety and tolerability of WTX101.

2.2 Endpoints

The primary endpoints are:

- Plasma concentrations and PK parameters (e.g., $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, Cmax, t_{max}, λ_z, and $t_{½}$, CL/F, and Vz/F) for total Molybdenum (Mo) following WTX101 EC tablet administration under fasting and fed conditions and WTX101 non coated capsule coadministered with a PPI under fasting conditions
- Safety and tolerability will be evaluated based on physical examinations, vital sign measurements, Electrocardiogram (ECGs), adverse events (AEs), and clinical laboratory tests.

3. STUDY DESIGN

This will be a single-center, open-label, randomized, 3-period, 3-treatment, 6-sequence crossover study evaluating the PK of single doses of WTX101 in healthy subjects based on the measurement of plasma total Mo.

Eighteen (18) healthy, non-tobacco using adult male and female subjects who complete the study screening assessments and meet all eligibility criteria will be enrolled. These subjects will receive the corresponding product, according to a randomization scheme generated at Celerion.

Screening of subjects will occur within 28 days prior to the first WTX101 dose.

Subjects randomized to receive PPI in Period 1 (Treatment C) will report to the Clinical Research Unit (CRU) on Day -5, i.e. 5 days prior to first dosing with WTX101, to receive a morning dose of omeprazole under fasting conditions. These subjects will be given a container with omeprazole doses and will continue once daily (QD) administration of omeprazole under fasting conditions on an outpatient basis, until their return to the CRU for check-in on Day -1. To ensure that the planned number of subjects are dosed with WTX101 on Day 1 of Period 1, stand-by subjects will also receive QD doses of omeprazole, as described above. Should any subject withdraw from the study after omeprazole administration, but before receiving WTX101 in Period 1, they will be replaced with a stand-by subject.

Subjects randomized to receive PPI in Periods 2 or 3 will receive the container with omeprazole doses prior to discharge from the CRU after the 192-hour post-dose procedures in Period 1 or Period 2, as appropriate. These subjects will initiate QD administration of omeprazole under fasting conditions at home the following day and continue until their return to the CRU for their next admission.

In each of the 3 periods, all subjects (Treatments A, B, and C) will be admitted to the CRU on Day -1, and will receive WTX101 EC tablets alone under fasting conditions (Treatment A); WTX101 EC tablets alone under fed conditions (Treatment B); or, omeprazole under fasting conditions followed by WTX101 non-coated capsules under fasting conditions (Treatment C). Pharmacokinetic (PK) sampling (for the measurement of plasma concentrations of total elemental Molybdenum (Mo)) will be obtained at the following timepoints while subjects remain in the CRU: Time 0 (within 1 hour predose), and then 1, 2, 3, 3.5, 4, 4.5, 5, 6, 7, 7.5, 8, 8.5, 9, 9.5, 10, 12, 14, 16, 24, 36, and 48 hours postdose. Subjects will be discharged on Day 3 following the 48 hours postdose procedures, unless medically necessary to extend confinement to 72 hours.

Subjects will be required to return to the CRU for outpatient visits on 6 consecutive days (Days 4, 5, 6, 7, 8 and 9) in each period, for subsequent PK sampling and procedures at: 72, 96, 120, 144, 168, and 192 hours postdose.

The washout between WTX101 doses in each period will be at least 14 days.

Subjects will return to the CRU 14 days (+/-2 days) after the final study medication administration for an end of study (EOS) visit with follow-up procedures, and to determine if any AE has occurred since the last study visit. Subjects who terminate the study early should be seen and assessed by an Investigator, whenever possible, to undergo the procedures associated with the EOS visit.

Safety will be monitored throughout the study.

Subjects who complete the study may be involved in the study for up to 48 days excluding screening (Day -5 of period one to the EOS visit).

Subjects may be replaced at the discretion of the Sponsor.

4. ANALYSIS POPULATIONS

4.1 Analysis Populations

Safety Population: All subjects who received at least one dose of the WTX101.

5. TREATMENT DESCRIPTIONS

5.1 Test Treatment

Treatment B: 60 mg WTX101 (2 x WTX101 EC tablets, 30mg) at Hour 0 on Day 1, 30 minutes after the start of a high-fat breakfast, preceded by an overnight fast.

Treatment C: 20 mg omeprazole (1 x 20 mg delayed-release capsule) QD on the mornings of Days -5 to -1 following an overnight fast, 20 mg omeprazole capsule at Hour -1 on Day 1 following an overnight fast, and 60 mg WTX101 (2 x WTX101 non-coated capsules, 30mg) at Hour 0 on Day 1

A brief treatment description will be used in tables and listings as:

Treatment B: 60 mg WTX101 on Day 1 (Fed).

Treatment C: 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at Hour 0 on Day 1 (Fasted)

5.2 Reference Treatment

Treatment A: 60 mg WTX101 (2 x WTX101 EC tablets, 30mg) at Hour 0 on Day 1 following an overnight fast

A brief treatment description will be used in tables and listings as:

Treatment A: 60 mg WTX101 on Day 1 (Fasted).

Treatments will be referred to in the text of the report as:

Treatment A (WTX101 alone, fasted), Treatment B (WTX101 alone, fed), and Treatment C (WTX101 with omeprazole, fasted).

6. PHARMACOKINETIC ANALYSIS

A separate pharmacokinetic analysis plan (PKAP) will be prepared by Kramer Consulting LLC and agreed upon with the Sponsor.

7. EFFICACY/PHARMACODYNAMICS

Not applicable

8. SAFETY

All clinical safety and tolerability data will be listed by subject and assessment timpoints, including rechecks, unscheduled assessments, and early termination, chronologically.

Continuous variables will be summarized using N, mean, standard deviation (SD), coefficient of variance (CV), median, minimum, and maximum. Frequency counts will be reported for all categorical data.

Decimal point will be presented as follows: N will be presented without decimal, minimum/maximum in same precision as in the database, mean/median in one more decimal than minimum/maximum, and SD in one more decimal than mean/median.

Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators.

No inferential statistics will be performed.

8.1 Subject Discontinuation

Individual subject's dosing status (treatment dosed) will be provided along with their completion status and date. Frequency counts of all subjects dosed in the study, completing the study, and discontinuing early from the study along with the reason for discontinuation will be tabulated by treatment sequence and overall for this presentation.

8.2 Demographics

Descriptive statistics will be calculated for continuous demographic variables (age, weight, height, and body mass index) and frequency counts will be tabulated for categorical demographic variables (gender, race, and ethnicity) by treatment sequence and overall.

8.3 Adverse Events

Adverse events (AEs) will be coded with Medical Dictionary for Regulatory Activities (MedDRA®) Version 16.1.

A treatment-emergent adverse event (TEAE) is defined as an AE that is starting or worsening at the time of or after study drug administration. An AE that occurs during the washout period between drugs is considered treatment emergent to the last drug given. If an AE that was reported during the study increases in severity that AE is given a resolution date and time and a new record initiated with the new severity. If the severity of an AE remains the same or decreases, the AE will be kept open through to resolution. All AEs captured in the database

will be listed in by-subject data listings. However, only TEAEs will be summarized. For treatment C, the TEAEs will be summarized by time interval (prior to WTX101 dosing and post WTX101 dosing) and overall.

Summary tables will include the number of subjects reporting the TEAE and percent of subjects who received study drug, number of TEAEs and percent of total TEAEs. These results will be summarized by treatment and overall. Number of subjects reporting at least one TEAE and number of TEAEs will also be summarized by treatment, severity (NCI CTCAE toxicity grading scale 5-point severity scale), and relationship to treatment. In addition, all AEs (preferred term) for all periods but exclude those who took Omeprazole in Period 1 (i.e. following first WTX101-101 dosing) will be summarized by the number and percentage of subjects with the same AE and also by severity and the relationship to drug. All AEs will be listed by subject, including verbatim term, onset date and time, resolved date and time, seriousness, severity, frequency, and relationship to treatment.

Should any serious adverse events (SAEs), AEs leading to discontinuation, and AEs resulting in death occur during this study, the AEs will be displayed in the data listings and discussed in the text of the study report.

8.4 Labs (Serum Chemistry, Hematology, Coagulation, and Urinalysis)

Serum chemistry, hematology, coagulation, and urinalysis will be performed at screening following a fast of at least 8 hours, the check-in for each period following a fast of at least 6 hours, 36 hour pose WTX101 dose in each period, and end of study (or upon early termination).

Descriptive statistics at specified time points (Check-in and 36 hour post WTX101 dose) will be provided for serum chemistry, hematology, coagulation, and urinalysis results by treatment. Change from Baseline [Check-in (Day -1) prior to WTX101 dosing] to the postdose time point (Hour 36) will also be provided for serum chemistry, hematology, coagulation, and urinalysis results for each treatment. Shift from baseline value tables, which provide the frequency of each shift in out of range results, will be provided by treatment for serum chemistry, hematology, coagulation, and urinalysis results. In addition, descriptive statistics at screening and end of study will be provided for serum chemistry, hematology, coagulation, and urinalysis results for all subjects as well.

All out-of-range values for serum chemistry, hematology, coagulation, and urinalysis will be listed by subject. Out-of-range values are considered to be values that are out-of normal range as defined by the clinical laboratory. The normal range values will be displayed in the data listings.

When change from baseline is calculated, baseline is the last schedule assessment before dosing of WTX101 in each period, also including rechecks and unscheduled assessments, whichever is later. Rechecks, unscheduled

assessments and early termination measurements taken after WTX101 dosing will not be used in the summarization.

Clinical laboratory values will also be displayed in a data listing by subject.

8.5 Vital Signs

Vital signs (blood pressure, heart rate, respiration rate, and body temperature) will be performed at screening, Check-in, predose, Hour 1, Hour 4, Hour 8, Hour 12, and Hour 24 post WTX101 dose for each period, and at the end of study (or upon early termination).

Descriptive statistics for vital sign measurements (blood pressure, heart rate, respiration rate, and body temperature) at specified time points (Check-in, predose, Hour 1, Hour 4, Hour 8, Hour 12, and Hour 24 post WTX101 dose) and change from Baseline to postdose observations will be provided for vital sign measurements by treatment. In addition, descriptive statistics at screening and end of study will be provided for vital sign measurements for all subjects as well.

When change from baseline is calculated, baseline is the last schedule assessment before dosing of WTX101 in each period, also including rechecks and unscheduled assessments, whichever is later. Rechecks, unscheduled assessments and early termination measurements taken after WTX101 dosing will not be used in the summarization.

Vital signs will also be displayed in a data listing by subject.

8.6 ECG

Single 12-lead ECG will be performed at screening, Check-in, predose, Hour 1, Hour 4, Hour 8, Hour 12, and Hour 24 post WTX101 dose for each period, and at the end of study (or upon early termination).

ECGs will be performed on subjects after at least 2 minutes in supine position. All ECG tracings will be reviewed by the Study Physician or his/her designee.

Descriptive statistics will be calculated for heart rate, PR, QRS, QT, QTcB and QTcF (Bazett's and Fridericia's correction) intervals by treatment at the specified time points (Check-in, predose, Hour 1, Hour 4, Hour 8, Hour 12, and Hour 24 post WTX101 dose) as well as change from baseline to the postdose time points. In addition, descriptive statistics at screening and end of study will be provided for vital sign measurements for all subjects as well.

When change from baseline is calculated, baseline is the last schedule assessment before dosing of WTX101 in each period, also including rechecks and unscheduled assessments, whichever is later. Rechecks, unscheduled

assessments and early termination measurements taken after WTX101 dosing will not be used in the summarization.

ECG results will be classified as normal, abnormal not clinically significant, or abnormal clinically significant by the Principal Investigator (PI). Frequency of ECG results shift from baseline will be provided at specified time points by treatment.

ECGs will also be displayed in a data listing by subject.

8.7 Concomitant Medications

All concomitant medications recorded during the study will be coded with the WHO Dictionary Version 01Sep2013.

8.8 Physical Examination

A full physical examination will be performed at screening, check-in, and at the end of the study or upon early termination. A symptom-driven physical examination may be performed at other times, at the PI's discretion. Physical examination will be presented in a data listing. A normal-abnormal shift table will also be presented for physical exam results. Abnormal findings will be discussed in the clinical study report.

9. SUMMARY TABLES AND FIGURES

Summary tables and figures are numbered following the ICH structure. Please note that all summary tables and figures will be generated using SAS® Version 9.3 or higher.

The following is a list of table numbers and titles that will be included as summary tables:

14.1 Demographic Data Summary Tables

Table 14.1.1	Summary of Disposition
Table 14.1.2	Disposition of Subjects
Table 14.1.3	Demographic Summary

14.2 Pharmacokinetic Data Summary Tables and Figures

Please note: This part will be covered by the separated PKAP.

14.3 Safety Data Summary Tables

14.3.1 Displays of Adverse Events

Table 14.3.1.1 Adverse Event Frequency by Treatment – Number of Subjects Reporting the Event (% of Subject Dosed)

Table 14.3.1.2 Adverse Event Frequency by Treatment – Number of Adverse Events (% of Total Adverse Events)

Table 14.3.1.3 Adverse Event Frequency by Treatment, Severity, and Relationship to Drug – Number of Subjects Reporting Events

Table 14.3.1.4 Adverse Event Frequency by Treatment, Severity, and Relationship to Drug – Number of Adverse Events

Table 14.3.1.5 Adverse Event Frequency by Severity and Relationship to Drug Following First WTX101-101 Dosing – Number of Subjects Reporting Events

Table 14.3.1.6 Adverse Event Frequency by Severity, and Relationship to Drug Following First WTX101-101 Dosing – Number of Adverse Events

14.3.2 Listings of Deaths, other Serious and Significant Adverse Events

Table 14.3.2.1 Serious Adverse Events (if no serious adverse event occurred, a statement 'No serious adverse event is reported' will be in the table.

14.3.3. Narratives of Deaths, other Serious and Certain other Significant Adverse Events

14.3.4. Abnormal Laboratory Value Listing (each patient)

Table 14.3.4.1 Out-of-Range Values and Recheck Results – Serum Chemistry

Table 14.3.4.2 Out-of-Range Values and Recheck Results – Hematology

Table 14.3.4.3 Out-of-Range Values and Recheck Results – Coagulation

Table 14.3.4.4 Out-of-Range Values and Recheck Results – Urinalysis

Table 14.3.4.5 Out-of-Range Values and Recheck Results – Other

14.3.5. Displays of Other Laboratory, Vital Signs, Electrocardiogram, Physical Examination, and Other Safety Data

Table 14.3.5.1 Clinical Laboratory Summary and Change from Baseline – Serum Chemistry

Table 14.3.5.2 Clinical Laboratory Shift from Baseline – Serum Chemistry

Table 14.3.5.3 Clinical Laboratory Summary and Change from Baseline – Hematology

Table 14.3.5.4 Clinical Laboratory Shift from Baseline – Hematology

10. DATA LISTING TITLES AND NUMBERS

Note: Hepatitis and HIV results that are provided by the clinical laboratory will not be presented in subject data listings and will not be included in any database transfer.

Data listings are numbered following the ICH structure. The following is a list of appendix numbers and titles that will be included as data listings:

16.1. Study Information

Appendix 16.1.10.1 Clinical Laboratory Reference Ranges

16.2. Subject Data Listings

16.2.1. Subject Discontinuation

Appendix 16.2.1 Subject Discontinuation

16.2.2. Protocol Deviations

Appendix 16.2.2 Protocol Deviations

16.2.3. Subjects Excluded from Pharmacokinetic Analysis

Appendix 16.2.3 Subjects Excluded from Pharmacokinetic Analysis

Note: Appendices 16.2.2 and 16.2.3 are generated in MS Word for inclusion in the study report

16.2.4. Demographic Data

Appendix 16.2.4.1 Demographics
Appendix 16.2.4.2.1 Physical Examination (I of II)
Appendix 16.2.4.2.2 Physical Examination (II of II)

16.2.5. Compliance and Drug Concentration Data

16.2.6. Individual Pharmacokinetic Data

Please note: This part will be covered by the separated PKAP.

16.2.7. Individual Adverse Event Listings

16.2.8. Individual Laboratory Measurements

16.2.9. Other Safety Observations

Appendix 16.2.9.3 Phone Participant

11. TABLE SHELLS

The following table shells provide a framework for the display of data from this study. The shells may change due to unforeseen circumstances. These shells may not be reflective of every aspect of this study, but are intended to show the general layout of the tables that will be included in the final report.

Table 14.1.1 Summary of Disposition

	Treatment Sequence						
Disposition	ABC	ACB	BAC	BCA	CAB	CBA	Overall
Dosed	XX	XX	XX	XX	XX	XX	XX
Completed	XX	XX	XX	XX	XX	XX	XX
Discontinued Early	X	X	X	X	X	X	X
<Discontinuation Reason>	X	X	X	X	X	X	X

Note: Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)
Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at Hour 0 on Day 1 (Fasted)

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Table 14.1.2 Disposition of Subjects

Subject Number	Randomized Dosing Sequence	Treatment Dosed			Treatment Completed			Study Completion	
		A	B	C	A	B	C	Status	Date
X	XXX	Yes	Yes	Yes	Yes	Yes	Yes	Completed Study	DDMMMYYYY
X	XXX	No	Yes	Yes	No	Yes	Yes	Terminated Study Prematurely	DDMMMYYYY
X	XXX	Yes	Yes	Yes	Yes	Yes	Yes	Completed Study	DDMMMYYYY
X	XXX	Yes	Yes	Yes	Yes	Yes	Yes	Completed Study	DDMMMYYYY
X	XXX	Yes	Yes	Yes	Yes	Yes	Yes	Completed Study	DDMMMYYYY
X	XXX	Yes	Yes	Yes	Yes	Yes	Yes	Completed Study	DDMMMYYYY
X	XXX	Yes	Yes	Yes	Yes	Yes	Yes	Completed Study	DDMMMYYYY
X	XXX	Yes	Yes	Yes	Yes	Yes	Yes	Completed Study	DDMMMYYYY
X	XXX	Yes	Yes	Yes	Yes	Yes	Yes	Completed Study	DDMMMYYYY
XX	XXX	Yes	Yes	Yes	Yes	Yes	Yes	Terminated Study Prematurely	DDMMMYYYY
XX	XXX	Yes	Yes	Yes	Yes	Yes	Yes	Completed Study	DDMMMYYYY
XX	XXX	Yes	Yes	Yes	Yes	Yes	Yes	Completed Study	DDMMMYYYY
XX	XXX	Yes	Yes	Yes	Yes	Yes	Yes	Completed Study	DDMMMYYYY
XX	XXX	Yes	Yes	Yes	Yes	Yes	Yes	Completed Study	DDMMMYYYY
XX	XXX	Yes	Yes	Yes	Yes	Yes	Yes	Completed Study	DDMMMYYYY
		XX	XX	XX	XX	XX	XX		

Note: Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)
Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at Hour 0 on Day 1 (Fasted)

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Table 14.1.3 Demographic Summary

		Treatment Sequence						
Trait		ABC	ACB	BAC	BCA	CAB	CBA	Overall
Gender	Female	XX	XX	XX	XX	XX	XX	XX
	Male	XX	XX	XX	XX	XX	XX	XX
Race	White	XX	XX	XX	XX	XX	XX	XX
	Black or African American	XX	XX	XX	XX	XX	XX	XX
	Asia	XX	XX	XX	XX	XX	XX	XX
Ethnicity	Hispanic or Latino	XX	XX	XX	XX	XX	XX	XX
	Not Hispanic or Latino	XX	XX	XX	XX	XX	XX	XX
Age	N	X	X	X	X	X	X	X
	Mean	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	SD	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
	Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	Minimum	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	Maximum	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X

Note: Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)
Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at Hour 0 on Day 1 (Fasted)

Program: /AAXXXXX/ECR/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.1.3 Demographic Summary

Trait		Treatment Sequence ABC	ACB	BAC	BCA	CAB	CBA	Overall
Weight (kg)	N	X	X	X	X	X	X	X
	Mean	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	SD	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
	Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	Minimum	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	Maximum	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Height (cm)	N	X	X	X	X	X	X	X
	Mean	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	SD	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
	Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	Minimum	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	Maximum	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Body Mass Index (kg/m^2)	N	X	X	X	X	X	X	X
	Mean	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	SD	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
	Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	Minimum	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	Maximum	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X

Note: Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)
Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at Hour 0 on Day 1 (Fasted)

Program: /AAXXXXX/ECR/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.3.1.1 Adverse Event Frequency by Treatment - Number of Subjects Reporting Events (% of Subjects Dosed)

	Treatment						
			C			Overall Following the First WTX101 Dosing	
Adverse Event*	A	B	Prior to WTX101 Dosing	Post WTX101 Dosing	Overall		Overall
Number of Subjects Dosed	XX (100%)	XX (100%)	XX (100%)	XX (100%)	XX (100%)	XX (100%)	XX (100%)
Number of Subjects With Adverse Events	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Number of Subjects Without Adverse Events	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
System Organ Class							
Preferred Term	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Preferred Term	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Preferred Term	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Preferred Term	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Preferred Term	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)

Note: * Adverse events are classified according to MedDRA Version 16.1. Each Subject was only counted once per preferred term.
Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)
Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at Hour 0 on Day 1 (Fasted)

Program: /AAXXXXX/ECR/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.3.1.2 Adverse Event Frequency by Treatment - Number of Adverse Events (% of Total Adverse Events)

	Treatment						
			C			Overall Following the First WTX101 Dosing	
Adverse Event*	A	B	Prior to WTX101 Dosing	Post WTX101 Dosing	Overall		Overall
Number of Adverse Events	XX (100%)	XX (100%)	XX (100%)	XX (100%)	XX (100%)	XX (100%)	XX(100%)
System Organ Class							
Preferred Term	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Preferred Term	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Preferred Term	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Preferred Term	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Preferred Term	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)

Note: * Adverse events are classified according to MedDRA Version 16.1.
Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)
Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at Hour 0 on Day 1 (Fasted)

Program: /AAXXXXX/ECR/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.3.1.3 Adverse Event Frequency by Treatment, Severity, and Relationship to Drug
- Number of Subjects Reporting Events

Adverse Event*	Treatment	Number of Subjects with Adverse Events	Severity Grade					Relationship to Drug				
			1	2	3	4	5	Likely	Probably	Possibly	Unlikely	Unrelated
Abdominal pain	A	X	X	X	X	X	X	X	X	X	X	X
Constipation	A	X	X	X	X	X	X	X	X	X	X	X
Headache	A	X	X	X	X	X	X	X	X	X	X	X
	B	X	X	X	X	X	X	X	X	X	X	X
Myalgia	A	X	X	X	X	X	X	X	X	X	X	X
Nasal congestion	C1	X	X	X	X	X	X	X	X	X	X	X
Skin laceration	C2	X	X	X	X	X	X	X	X	X	X	X
Treatment A		X	X	X	X	X	X	X	X	X	X	X
Treatment B		X	X	X	X	X	X	X	X	X	X	X
Treatment C1		X	X	X	X	X	X	X	X	X	X	X
Treatment C2		X	X	X	X	X	X	X	X	X	X	X
Treatment C		X	X	X	X	X	X	X	X	X	X	X
Overall		X	X	X	X	X	X	X	X	X	X	X

Note: * Adverse events are classified according to MedDRA Version 16.1.
When a subject experienced the same AE at more than one level of severity during a treatment period, only the most severe one was counted. When a subject experienced the same AE at more than one level of drug relationship during a treatment period, only the most related one was counted.
Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Severe, Grade 4 = Life-threatening, Grade 5 = Death due to AE.
Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)
Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at Hour 0 on Day 1 (Fasted)
Treatment C1 = Treatment C prior to WTX101 dosing, Treatment C2 = Treatment C post WTX101 dosing

Program: /AAXXXXX/ECR/sas_prg/stsas/tab tblae3a_auto.sas DDMMMYYYY HH:MM

Table 14.3.1.4 Adverse Event Frequency by Treatment, Severity, and Relationship to Drug - Number of Adverse Events

Adverse Event*	Treatment	Number of Adverse Events	Severity Grade					Relationship to Drug				
			1	2	3	4	5	Likely	Probably	Possibly	Unlikely	Unrelated
Abdominal pain	A	X	X	X	X	X	X	X	X	X	X	X
Constipation	A	X	X	X	X	X	X	X	X	X	X	X
Headache	A	X	X	X	X	X	X	X	X	X	X	X
	B	X	X	X	X	X	X	X	X	X	X	X
Myalgia	A	X	X	X	X	X	X	X	X	X	X	X
Nasal congestion	C1	X	X	X	X	X	X	X	X	X	X	X
Skin laceration	C2	X	X	X	X	X	X	X	X	X	X	X
Treatment A		X	X	X	X	X	X	X	X	X	X	X
Treatment B		X	X	X	X	X	X	X	X	X	X	X
Treatment C1		X	X	X	X	X	X	X	X	X	X	X
Treatment C2		X	X	X	X	X	X	X	X	X	X	X
Treatment C		X	X	X	X	X	X	X	X	X	X	X
Overall		X	X	X	X	X	X	X	X	X	X	X

Note: * Adverse events are classified according to MedDRA Version 16.1.
Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Severe, Grade 4 = Life-threatening, Grade 5 = Death due to AE.
Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)
Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at Hour 0 on Day 1 (Fasted)
Treatment C1 = Treatment C prior to WTX101 dosing, Treatment C2 = Treatment C post WTX101 dosing

Program: /AAXXXXX/ECR/sas_prg/stsas/tab tblae4a_auto.sas DDMMMYYYY HH:MM

Table 14.3.1.5 Adverse Event Frequency by Severity and Relationship to Drug Following First WTX101-101 Dosing - Number of Subjects Reporting Events

Adverse Event*	Number of Subjects with Adverse Events	Severity Grade					Relationship to Drug				
		1	2	3	4	5	Likely	Probably	Possibly	Unlikely	Unrelated
Abdominal pain	X	X	X	X	X	X	X	X	X	X	X
Constipation	X	X	X	X	X	X	X	X	X	X	X
Headache	X	X	X	X	X	X	X	X	X	X	X
	X	X	X	X	X	X	X	X	X	X	X
Myalgia	X	X	X	X	X	X	X	X	X	X	X
Nasal congestion	X	X	X	X	X	X	X	X	X	X	X
Skin laceration	X	X	X	X	X	X	X	X	X	X	X
Overall	X	X	X	X	X	X	X	X	X	X	X

Note: * Adverse events are classified according to MedDRA Version 16.1.
When a subject experienced the same AE at more than one level of severity during a treatment period, only the most severe one was counted. When a subject experienced the same AE at more than one level of drug relationship during a treatment period, only the most related one was counted.
Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Severe, Grade 4 = Life-threatening, Grade 5 = Death due to AE.

Program: /AAXXXXX/ECR/sas_prg/stsas/tab tblae3a_auto.sas DDMMMYYYY HH:MM

Table 14.3.1.6 Adverse Event Frequency by Severity and Relationship to Drug Following First WTX101-101 Dosing - Number of Adverse Events

Adverse Event*	Number of Adverse Events	Severity Grade					Relationship to Drug				
		1	2	3	4	5	Likely	Probably	Possibly	Unlikely	Unrelated
Abdominal pain	X	X	X	X	X	X	X	X	X	X	X
Constipation	X	X	X	X	X	X	X	X	X	X	X
Headache	X	X	X	X	X	X	X	X	X	X	X
	X	X	X	X	X	X	X	X	X	X	X
Myalgia	X	X	X	X	X	X	X	X	X	X	X
Nasal congestion	X	X	X	X	X	X	X	X	X	X	X
Skin laceration	X	X	X	X	X	X	X	X	X	X	X
Overall	X	X	X	X	X	X	X	X	X	X	X

Note: * Adverse events are classified according to MedDRA Version 16.1.
Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Severe, Grade 4 = Life-threatening, Grade 5 = Death due to AE.

Program: /AAXXXXX/ECR/sas_prg/stsas/tab tblae4a_auto.sas DDMMMYYYY HH:MM

Table 14.3.2.1 Serious Adverse Events

No serious adverse event is reported during the study.

Program: /AAXXXXX/ECR/sas_prg/stsas/tab cdash_tblae_ser.sas DDMMMYYYY HH:MM

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Table 14.3.4.1 Out-of-Range Values and Recheck Results - Serum Chemistry

Subject Number	Age/ Gender	Study Period	Treatment	Day	Hour	Date	Test Name X.X-XX.X (mg/dL)	Test Name X.X-X.X (mEq/L)	Test Name XXX-XXX (mEq/L)	Test Name X.X-X (g/dL)	Test Name F: X-XX M: X-XX (mg/dL)
X	XX/M	Screen				DDMMMYYYY	X.X	X.X LN	XXX	X.X	XX
		1	A	-X	-X.X	DDMMMYYYY	X.X	X.X LN	XXX	X.X	XX
				X	X.X	DDMMMYYYY	X.X	X.X LN	XXX	X.X	XX
		2	B	-X	-X.X	DDMMMYYYY	X.X	X.X LN	XXX	X.X	XX
				X	X.X	DDMMMYYYY	X.X	X.X LN	XXX	X.X	XX

Note: H = Above Normal Range, L = Below Normal Range
Computer: N = Not Clinically Significant, Y = Clinically Significant
PI interpretation: - = Not Clinically Significant
Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)
Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at Hour 0 on Day 1 (Fasted)

Program: /AAXXXXX/ECR/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Please note that Table 14.3.4.2-5 will resemble 14.3.4.1.

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Table 14.3.5.1 Clinical Laboratory Summary and Change From Baseline - Serum Chemistry

					Treatment			Change From Baseline		
Laboratory Test (unit)	Normal Range	Time point	Statistic	Overall	A	B	C	A	B	C
Test Name (unit)	XX.X – XX.X	Screen	N	XX						
			Mean	X.XX						
			SD	X.XXX						
			CV	X.XXX						
			Median	X.XX						
			Minimum	X.X						
			Maximum	XX.X						
		Baseline	N		XX	XX	XX			
			Mean		X.XX	X.XX	X.XX			
			SD		X.XXX	X.XXX	X.XXX			
			CV		X.XXX	X.XXX	X.XXX			
			Median		X.XX	X.XX	X.XX			
			Minimum		X.X	X.X	X.X			
			Maximum		XX.X	XX.X	XX.X			
		Hour 36	N		XX	XX	XX	XX	XX	XX
			Mean		X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
			SD		X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX
			CV		X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX
			Median		X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
			Minimum		X.X	X.X	X.X	X.X	X.X	X.X
			Maximum		XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
		End of Study	N	XX						
			Mean	X.XX						
			SD	X.XXX						
			CV	X.XXX						
			Median	X.XX						
			Minimum	X.X						
			Maximum	XX.X						

<Similar for remaining tests.>

Note: Baseline is the last observation, including rechecks, obtained prior to dosing of WTX101 in the treatment period.
Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)

```
      Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at
                    Hour 0 on Day 1 (Fasted)


Program:  /AAXXXXX/ECR/sas_prg/stsas/tab_PROGRAMNAME.sas  DDMMMYYYY  HH:MM
```

Please note that Tables 14.3.5.3, 14.3.5.5, and 14.3.5.7 will resemble 14.3.5.1.

Table 14.3.5.2 Clinical Laboratory Shift From Baseline - Serum Chemistry

Laboratory Test	Normal Range	Time Point	Treatment	Baseline* L: Postdose L	Baseline* L: Postdose N	Baseline* L: Postdose H	Baseline* N: Postdose L	Baseline* N: Postdose N	Baseline* N: Postdose H	Baseline* H: Postdose L	Baseline* H: Postdose N	Baseline* H: Postdose H
Test Name (units)	XX-XXX	Hour 36	A	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)
			B	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)
			C	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)

<Similar for remaining laboratory tests and time points>

Note: L = Below Normal Range, N = Within Normal Range, H = Above Normal Range.
* Baseline is the last observation, including rechecks, obtained prior to dosing of WTX101 in the treatment period.
The percentage are based on the number of subjects within the test*treatment*timepoint.
Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)
Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at Hour 0 on Day 1 (Fasted)

Program: /AAXXXXX/ECR/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Please note that Tables 14.3.5.4 and 14.3.5.6 will resemble 14.3.5.2.

Table 14.3.5.8 Clinical Laboratory Shift From Baseline - Urinalysis

Laboratory Test	Normal Range	Time Point	Treatment	Baseline* N: Postdose N	Baseline* N: Postdose O	Baseline* O: Postdose N	Baseline* O: Postdose O
Test Name (units)	XX-XXX	Hour 36	A	X (X%)	X (X%)	X (X%)	X (X%)
			B	X (X%)	X (X%)	X (X%)	X (X%)
			C	X (X%)	X (X%)	X (X%)	X (X%)

<Similar for remaining laboratory tests and time points>

Note: N = Within Normal Range, O = Outside Normal Range.
* Baseline is the last observation, including rechecks, obtained prior to dosing of WTX101 in the treatment period.
The percentage are based on the number of subjects within the test*treatment*timepoint.
Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)
Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at Hour 0 on Day 1 (Fasted)

Program: /AAXXXXX/ECR/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.3.5.9 Vital Sign Summary and Change From Baseline

				Treatment			Change From Baseline		
Measurement (unit)	Time point	Statistic	Overall	A	B	C	A	B	C
Test Name (unit)	Screen	N	XX						
		Mean	X.XX						
		SD	X.XXX						
		CV	X.XXX						
		Median	X.XX						
		Minimum	X.X						
		Maximum	XX.X						
	Check-in	N		XX	XX	XX			
		Mean		X.XX	X.XX	X.XX			
		SD		X.XXX	X.XXX	X.XXX			
		CV		X.XXX	X.XXX	X.XXX			
		Median		X.XX	X.XX	X.XX			
		Minimum		X.X	X.X	X.X			
		Maximum		XX.X	XX.X	XX.X			
	Baseline	N		XX	XX	XX			
		Mean		X.XX	X.XX	X.XX			
		SD		X.XXX	X.XXX	X.XXX			
		CV		X.XXX	X.XXX	X.XXX			
		Median		X.XX	X.XX	X.XX			
		Minimum		X.X	X.X	X.X			
		Maximum		XX.X	XX.X	XX.X			
	Hour 1	N		XX	XX	XX	XX	XX	XX
		Mean		X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		SD		X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX
		CV		X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX
		Median		X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		Minimum		X.X	X.X	X.X	X.X	X.X	X.X
		Maximum		XX.X	XX.X	XX.X	XX.X	XX.X	XX.X

<Similar for remaining time points and measurements. For the end of study time point, all subjects will be pooled together as overall as for screen time point.>

Note: Baseline is the last observation, including rechecks, obtained prior to dosing of WTX101 in the treatment period.
Treatment A = 60 mg WTX101 on Day 1 (Fasted)

```
       Treatment B = 60 mg WTX101 on Day 1 (Fed)
       Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at
                     Hour 0 on Day 1 (Fasted)

Program:  /AAXXXXX/ECR/sas_prg/stsas/tab_PROGRAMNAME.sas  DDMMMYYYY  HH:MM
```

Table 14.3.5.10 12-Lead Electrocardiogram Summary and Change From Baseline

				Treatment			Change From Baseline		
Parameter (unit)	Time point	Statistic	Overall	A	B	C	A	B	C
Heart Rate (bpm)	Screen	N	XX						
		Mean	X.XX						
		SD	X.XXX						
		CV	X.XXX						
		Median	X.XX						
		Minimum	X.X						
		Maximum	XX.X						
	Check-in	N		XX	XX	XX			
		Mean		X.XX	X.XX	X.XX			
		SD		X.XXX	X.XXX	X.XXX			
		CV		X.XXX	X.XXX	X.XXX			
		Median		X.XX	X.XX	X.XX			
		Minimum		X.X	X.X	X.X			
		Maximum		XX.X	XX.X	XX.X			
	Baseline	N		XX	XX	XX			
		Mean		X.XX	X.XX	X.XX			
		SD		X.XXX	X.XXX	X.XXX			
		CV		X.XXX	X.XXX	X.XXX			
		Median		X.XX	X.XX	X.XX			
		Minimum		X.X	X.X	X.X			
		Maximum		XX.X	XX.X	XX.X			
	Hour 1	N		XX	XX	XX	XX	XX	XX
		Mean		X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		SD		X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX
		CV		X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX
		Median		X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		Minimum		X.X	X.X	X.X	X.X	X.X	X.X
		Maximum		XX.X	XX.X	XX.X	XX.X	XX.X	XX.X

<Similar for remaining time points and parameters. For the end of study time point, all subjects will be pooled together as overall as for screen time point.>

Note: Baseline is the last non-missing measurement, including rechecks, obtained prior to dosing of WTX101 in the treatment period.
Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)

```
      Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at
                    Hour 0 on Day 1 (Fasted)

Program:  /AAXXXXX/ECR/sas_prg/stsas/tab_PROGRAMNAME.sas  DDMMMYYYY  HH:MM
```

Table 14.3.5.11 12-Lead Electrocardiogram Shift From Baseline

		Baseline = N			Baseline = ANCS			Baseline = ACS		
		Postdose			Postdose			Postdose		
Treatment	Time Point	N	ANCS	ACS	N	ANCS	ACS	N	ANCS	ACS
A	Hour 1	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)
	Hour 4	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)
	Hour 8	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)
	Hour 12	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)
	Hour 24	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)
B	Hour 1	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)
	Hour 4	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)
	Hour 8	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)
	Hour 12	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)
	Hour 24	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)
C	Hour 1	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)
	Hour 4	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)
	Hour 8	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)
	Hour 12	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)
	Hour 24	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)	X (X%)	XX (XX%)	X (X%)

Note: N = Normal, ANCS = Abnormal, Not Clinically Significant, ACS = Abnormal, Clinically Significant
Baseline is last non-missing measurements, including rechecks, obtained prior to dosing of WTX101 in the treatment period.
Percentages are based on total number of observations for each treatment at each time point.
Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)
Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at Hour 0 on Day 1 (Fasted)

Program: /AAXXXXX/ECR/sas_prg/stsas/tab ecgshift.sas DDMMMYYYY HH:MM

Table 14.3.5.12 Physical Examination Shift From Screening

		Screen = Normal		Screen = Abnormal	
		During Study		During Study	
System	Time Point	Normal	Abnormal	Normal	Abnormal
XXXXXXX	Period 1 Check-in	X	X	X	X
	Period 2 Check-in	X	X	X	X
	Period 3 Check-in	X	X	X	X
	End of Study	X	X	X	X
XXXXXXX	Period 1 Check-in	X	X	X	X
	Period 2 Check-in	X	X	X	X
	Period 3 Check-in	X	X	X	X
	End of Study	X	X	X	X
XXXXXXX	Period 1 Check-in	X	X	X	X
	Period 2 Check-in	X	X	X	X
	Period 3 Check-in	X	X	X	X
	End of Study	X	X	X	X

Program: /AAXXXXX/ECR/sas_prg/stsas/tab ecgshift.sas DDMMMYYYY HH:MM

12. LISTING SHELLS

The following listing shells provide a framework for the display of data from this study. The shells may change due to unforeseen circumstances. These shells may not be reflective of every aspect of this study, but are intended to show the general layout of the listings that will be included in the final report.

Appendix 16.1.10.1 Clinical Laboratory Reference Ranges

Laboratory Group	Test Name	Gender	Age Category	Normal Range	Unit
Serum Chemistry	Test Name	<>	<>	XX - XX	units
	Test Name	<>	<>	XX - XX	units
	Test Name	<>	<>	XX - XX	units
	Test Name	<>	<>	XX - XX	units
	Test Name	<>	<>	XX - XX	units
	Test Name	<>	<>	XX - XX	units
Hematology	Test Name	<>	<>	XX - XX	units
	Test Name	<>	<>	XX - XX	units
	Test Name	<>	<>	XX - XX	units
	Test Name	<>	<>	XX - XX	units
	Test Name	<>	<>	XX - XX	units
<similar for remaining Laboratory Groups and Test Names>					

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.1 Subject Discontinuation

Subject Number	Study Period	Date	Completed Study?	Reason for Discontinuation	Comment
X	Post	DDMMMYYYY	Yes		
X	Post	DDMMMYYYY	Yes		
X	Post	DDMMMYYYY	Yes		
X	Post	DDMMMYYYY	Yes		
X	Post	DDMMMYYYY	No	Personal Reason	
X	Post	DDMMMYYYY	Yes		
X	Post	DDMMMYYYY	Yes		
X	Post	DDMMMYYYY	Yes		

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.1 Demographics

Subject Number	Date Of Birth	Age (yrs)	Gender	Race	Ethnicity	Height (cm)	Weight (kg)	BMI (kg/m^2)	Informed Consent Date
X	DDMMMYYYY	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XX.X	XXX.X	XX.XX	DDMMMYYYY
X	DDMMMYYYY	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XX.X	XXX.X	XX.XX	DDMMMYYYY
X	DDMMMYYYY	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XX.X	XXX.X	XX.XX	DDMMMYYYY
X	DDMMMYYYY	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XX.X	XXX.X	XX.XX	DDMMMYYYY
X	DDMMMYYYY	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XX.X	XXX.X	XX.XX	DDMMMYYYY
X	DDMMMYYYY	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XX.X	XXX.X	XX.XX	DDMMMYYYY
X	DDMMMYYYY	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XX.X	XXX.X	XX.XX	DDMMMYYYY

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.2.1 Physical Examination (I of II)

Subject Number	Study Period	Day	Hour	Date	Was PE Performed?	System1	System2	System3	System4	System5
X	Screen	.	.	DDMMMYYYY	YES	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL
	X	X	X	DDMMMYYYY	YES	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL

Note: * = See Appendix 16.2.4.2.3 Physical Examination Description.
HEENT = Head, Eyes, Ears, Nose, Throat.

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.2.2 Physical Examination (II of II)

Subject Number	Study Period	Day	Hour	Date	System6	System7	System8	System9	Etc.
X	Screen	.	.	DDMMMYYYY	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL
	X	X	X	DDMMMYYYY	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL

Note: * = See Appendix 16.2.4.2.3 Physical Examination Descriptions.

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.2.3 Physical Examination Descriptions

Subject Number	Study Period	Day	Hour	Date	Result	System	Description or Comment
X	Screen	.	.	DDMMMYYYY	ABNORMAL	Skin	RIGHT CHEST SCAR-NCS
X	Screen	.	.	DDMMMYYYY	ABNORMAL	Skin	ABDOMINAL SCAR-NCS
X	Screen	.	.	DDMMMYYYY	ABNORMAL	Skin	ABDOMINAL SCAR-NCS
XX	X	X	X	DDMMMYYYY	ABNORMAL	Skin	ABDOMINAL SCAR-NCS
XX	Screen	.	.	DDMMMYYYY	ABNORMAL	Back	MILD SCOLIOSIS-NCS

Note: HEENT = Head, Eyes, Ears, Nose, Throat, NCS = Not Clinically Significant.

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.3 Medical History

Subject Number	Any History?	Study Period	System Reviewed	Category	Date Start	Date End	Ongoing?	Condition or Event
X	XXX	Screen	XXXXXX XXXXX	Medical	DDMMMYYYY		YES	XXXXXXX XXXXXX XXXXXXXX
				Surgical	DDMMMYYYY	DDMMMYYYY	NO	
X	XXX	Screen	XXXXXXXX XXXXX	Medical	DDMMMYYYY	DDMMMYYYY	NO	

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.4 Substance Use

Subject Number	Study Period	Substance	Description of Use	Start Date	End Date	Description
X	Screen	XXXXXXXX XXX	XXXXX XXXXXXX XXXXXX	MMYYYY	<added if end date is different from start date >	XXXXXXXXXX XXXXXX XXXX

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.1.1 Inclusion Criteria

X. < >?
X. < >?
X. < >?
X. < >?
X. < >?
X. < >?
X. < >?
X. < >?
X. < >?

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.1.2 Exclusion Criteria

X. < >?
X.
X.
X.
X.
X.
X.
X.
X.
XX.
XX.
XX.
XX.
XX.
XX.

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.2 Subject Eligibility

Subject Number	Study Period	Did subject meet all eligibility criteria?	Criterion Not Met*	Specify
X	Screen	No	EXCLUSION X	XXXXXXXXXXXXXX XXXX
X	Screen	Yes		
X	Screen	Yes		
X	Screen	No	INCLUSION X	XXXXXXXXXX XXXXXXXXX

Note: * = Please refer to Appendices 16.2.5.1.1 and 16.2.5.1.2 for specific inclusion and exclusion criteria.

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.3.1 Check-in and Return Criteria

X. < >?
X. IF (Y)ES TO ANY QUESTION, WAS SUBJECT APPROVED FOR STUDY?

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.3.2 Check-in and Return Responses

Subject Number	Study Period	Date	Check-in Criteria X	Check-in Criteria X	Comment
X	X	DDMMMYYYY	No	N/A	Will only be present and populated if there is a comment present in the study database.
	X	DDMMMYYYY	No	N/A	
	X	DDMMMYYYY	No	N/A	
X	X	DDMMMYYYY	No	N/A	
	X	DDMMMYYYY	No	N/A	
	X	DDMMMYYYY	No	N/A	
X	X	DDMMMYYYY	No	N/A	
	X	DDMMMYYYY	No	N/A	
	X	DDMMMYYYY	No	N/A	

Note: N/A = Not Applicable.

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.3.3 Check-out Date and Time

Subject Number	Study Period	Check-out Date	Check-out Time	Comment
X	X	DDMMMYYYY	HH:MM	
	X	DDMMMYYYY	HH:MM	
	X	DDMMMYYYY	HH:MM	
X	X	DDMMMYYYY	HH:MM	
	X	DDMMMYYYY	HH:MM	
	X	DDMMMYYYY	HH:MM	
X	X	DDMMMYYYY	HH:MM	
	X	DDMMMYYYY	HH:MM	
	X	DDMMMYYYY	HH:MM	

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.4.1 Test Compound Description

Compound	Form	Route
XXXXXXXXXXXXX	< >	XXXX
XXXXXXXXXXXXX	< >	XXXX

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.4.2 Test Compound Administration Times

Subject Number	Study Period	Treatment	Day	Hour	Date	Actual Time	Compound	Dosage	Did You Fast?	Comments
X	X	X	X	X.X	DDMMMYYYY	X:XX:XX	XXXXXXXXX	< >	XXX	
	X	X	X	X.X	DDMMMYYYY	X:XX:XX	XXXXXXXXX	< >	XXX	
	X	X	X	X.X	DDMMMYYYY	X:XX:XX	XXXXXXXXX	< >	XXX	
		X	X	X.X	DDMMMYYYY	X:XX:XX	XXXXXXXXX	< >	XXX	
		X	X	X.X	DDMMMYYYY	X:XX:XX	XXXXXXXXX	< >	XXX	

Note: Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)
Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at Hour 0 on Day 1 (Fasted)

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

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Appendix 16.2.5.4.3 Drug and Diary Accountability

Subject Number	Study Period	Date	Time	(1) Diary?	If no, Comment	(2) Dispense Test Compounds?	(3) Condition of Test Compound/ Turn in Diary?	Treatment	Comments
X	ALL	DDMMMYYYY	X:XX:XX	XXX		XXX	XXX	X	
X	ALL	DDMMMYYYY	X:XX:XX	XXX		XXX	XXX	X	
X	ALL	DDMMMYYYY	X:XX:XX	XXX		XXX	XXX	X	

Note: (1) Was the subject given the test compound, dosing diary and instructions?
(2) Was the subject instructed to take the doses as directed on the drug packaging at their scheduled time with 240 mL of water?
(3) Did the subject return their diary and test compound container (empty or not)?
Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)
Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at Hour 0 on Day 1 (Fasted)

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.5 Blood Draw Times

Subject Number	Study Period	Treatment	Day	Hour	Date	Actual Time	Bioassay	Comments
X	X	X	X	-X.XX	DDMMMYYYY	X:XX:XX	XXXXXXXXXX	
				X.XX	DDMMMYYYY	X:XX:XX	XXXXXXXXXX	
				X.XX	DDMMMYYYY	X:XX:XX	XXXXXXXXXX	
				X.XX	DDMMMYYYY	XX:XX:XX	XXXXXXXXXX	
				X.XX	DDMMMYYYY	XX:XX:XX	XXXXXXXXXX	
				X.XX	DDMMMYYYY	XX:XX:XX	XXXXXXXXXX	
				X.XX	DDMMMYYYY	XX:XX:XX	XXXXXXXXXX	
				XX.XX	DDMMMYYYY	XX:XX:XX	XXXXXXXXXX	
				XX.XX	DDMMMYYYY	XX:XX:XX	XXXXXXXXXX	
			X	XX.XX	DDMMMYYYY	X:XX:XX	XXXXXXXXXX	
				XX.XX	DDMMMYYYY	X:XX:XX	XXXXXXXXXX	
				XX.XX	DDMMMYYYY	XX:XX:XX	XXXXXXXXXX	
			X	XX.XX	DDMMMYYYY	X:XX:XX	XXXXXXXXXX	

Note: Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)
Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at Hour 0 on Day 1 (Fasted)

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.6 Meal Times

Subject Number	Study Period	Treatment	Day	Hour	Event	Date	Start Time	Stop Time	Time Interval (Start HR to Stop HR)	Comments
X	X	X	-X	-XX.X	SNACK	DDMMMYYYY	XX:XX:XX	XX:XX:XX		
			X	X.X	BREAKFAST	DDMMMYYYY	XX:XX:XX	XX:XX:XX	X.X to X.X	
				X.X	LUNCH	DDMMMYYYY	XX:XX:XX	XX:XX:XX		
				X.X	DINNER	DDMMMYYYY	XX:XX:XX	XX:XX:XX		
				XX.X	SNACK	DDMMMYYYY	XX:XX:XX	XX:XX:XX		

Note: Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)
Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at Hour 0 on Day 1 (Fasted)

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

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Appendix 16.2.5.7 Concomitant Medications

Subject Number	Study Period	Treatment	Medication (WHO* Term)	Dosage	Route	Start Date	Start Time	Stop Date	Stop Time	Frequency	Indication	Continuing?
X	Screen		None									
	1	X	ACETAMINOPHEN (ACETAMINOPHEN)	620 mg	ORAL	DDMMMYYYY	HH:MM	HH:MM	DDMMMYYYY	Once	Toothache	No

Note: Concomitant medications are coded with WHO Dictionary Version 01SEP2013.
Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)
Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at Hour 0 on Day 1 (Fasted)

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.7.1 Adverse Events (I of II)

Subject Number	Study Period	Treat-ment	TE?^	Adverse Event*	Preferred Term	Time from Last Dose (DD:HH:MM)	Onset Date	Onset Time	Resolved Date	Resolved Time	Duration (DD:HH:MM)
PPD	Screen 1	X	Yes	None XXXXXXXXXXXXX	XXXXXXXXXX XXXXXXX	XX:XX:XX	DDMMMYYYY	X:XX	DDMMMYYYY	X:XX	XX:XX:XX

Note: ^ = Abbreviation for treatment-emergent, * = Adverse events are classified according to the MedDRA Version 16.1.
Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)
Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at Hour 0 on Day 1 (Fasted)
Treatment C1 = Treatment C prior to WTX101 dosing, Treatment C2 = Treatment C post WTX101 dosing

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

<Programmer Note: For treatment C, the AEs will be classified based on the onset date/time as prior to or post WTX101 dosing, notes as C1 and C2).

Appendix 16.2.7.2 Adverse Events (II of II)

Subject Number	Study Period	Treatment	Adverse Event	Onset Date	Onset Time	Freq	Severity	Ser*	Outcome	Relationship to Study Drug	Action
PPD	Screen 1	X	None XXXXXXXXXXXXXXXXXX	DDMMMYYYY	X:XX	Inter.	Grade 1	NS	Resolved	XXXXXXXX	None

Note: Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)
Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at Hour 0 on Day 1 (Fasted)
Treatment C1 = Treatment C prior to WTX101 dosing, Treatment C2 = Treatment C post WTX101 dosing
Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Severe, Grade 4 = Life-threatening, Grade 5 = Death due to AE.
Ser* represents Serious: NS = Not Serious
Freq represents Frequency: SI = Single Episode, Inter. = Intermittent, Cont. = Continuous

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

<Programmer Note: For treatment C, the AEs will be classified based on the onset date/time as prior to or post WTX101 dosing, notes as C1 and C2).

Appendix 16.2.7.3 Adverse Event Non-Medication Procedures

Subject Number	Study Period	Treatment	Adverse Event	Onset Date	Onset Time	Procedure Given Date	Procedure Given Time	Procedure Given Description
X	X	X	DRY LIPS	DDMMMYYYY	XX:XX	DDMMMYYYY	XX:XX	PETROLEUM JELLY
X	X	X	CONSTIPATION	DDMMMYYYY	XX:XX	DDMMMYYYY	XX:XX	PRUNE JUICE

Note: Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)
Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at Hour 0 on Day 1 (Fasted)
Treatment C1 = Treatment C prior to WTX101 dosing, Treatment C2 = Treatment C post WTX101 dosing

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

<Programmer Note: For treatment C, the AEs will be classified based on the onset date/time as prior to or post WTX101 dosing, notes as C1 and C2).

Appendix 16.2.7.4 Adverse Event Preferred Term Classification

Subject Number	Study Period	Treatment	Adverse Event	Preferred Term	Body System	Onset Date	Onset Time
PPD	1	X	XXXXXXX XXXXX XXXX XXXXXX	XXXXXXXXXX XXXXXXX	XXXXXXXXXXXXXXXXXXXX	DDMMMYYYY	X:XX

Note: * Adverse events are classified according to the MedDRA Version 16.1.
Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)
Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at Hour 0 on Day 1 (Fasted)
Treatment C1 = Treatment C prior to WTX101 dosing, Treatment C2 = Treatment C post WTX101 dosing

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

<Programmer Note: For treatment C, the AEs will be classified based on the onset date/time as prior to or post WTX101 dosing, notes as C1 and C2).

Appendices 16.2.8.2 to 16.2.8.6 will have the following format.

Appendix 16.2.8.1 Clinical Laboratory Report – Serum Chemistry

Subject Number	Age/ Gender	Study Period	Treatment	Hour	Date	Parameter1 < Range> (Unit)	Parameter2 < Range> (Unit)	Parameter3 < Range> (Unit)	Parameter4 < Range> (Unit)	Parameter5 < Range> (Unit)	Parameter6 < Range> (Unit)
X	XX	Screen		.	DDMMMYYYY	XX HN	XX	XX	XX	XX HN	XX
	XX	X	X		DDMMMYYYY	XX LY	XX LN	XX	XX LY	XX	XX

Programmer Note: Replace Parameter1, 2 etc. with actual lab tests in the study.

Note: H = Above Reference Range, L = Below Reference Range
Computer: N = Not Clinically Significant, Y = Clinically Significant
PI Interpretation: - = Not Clinically Significant, R = To be Rechecked, ^ = Will be Retested at a Later Event
Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)
Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at Hour 0 on Day 1 (Fasted)

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.7 Clinical Laboratory Report - Comments

Subject Number	Study Period	Treatment	Hour	Date	Department	Test	Result	Unit	Comment
X	X	X	-X.X	DDMMMYYYY	Other Tests	Fibrinogen	XXX	mg/dL	Not significant in the context of this study.

Note: Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)
Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at Hour 0 on Day 1 (Fasted)

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.9.1 Vital Signs

Subject Number	Study Period	Treatment	Day	Hour	Date	Time	Blood Pressure (mmHg) Test	Arm	Systolic/Diastolic	Pulse (bpm)	Respiration (rpm)	Temperature (C)	Weight (kg)	Comments
X	Screen		.	.	DDMMMYYYY	X:XX:XX							XXX.X	
			.	.	DDMMMYYYY	X:XX:XX	SITX	Right	XXX/ XX	XX	XX	XX.X		
	X	X	-X	-XX.X	DDMMMYYYY	XX:XX:XX	SITX	Right	XXX/ XX	XX	XX	XX.X		
			X	-X.X	DDMMMYYYY	X:XX:XX	SITX	Right	XXX/ XX	XX	XX	XX.X		
				X.X	DDMMMYYYY	X:XX:XX	SITX	Right	XXX/ XX	XX	XX	XX.X		
				XX.X	DDMMMYYYY	XX:XX:XX	SITX	Right	XXX/ XX	XX	XX	XX.X		

Note: SITX = X-minute sitting, R = Recheck Value.
Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)
Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at Hour 0 on Day 1 (Fasted)

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

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Appendix 16.2.9.2 12-Lead Electrocardiogram

Subject Number	Study Period	Treatment	Day	Hour	Date	Time	Result	Heart Rate (bpm)	PR (msec)	QRS (msec)	QT (msec)	QTCB* (msec)	QTCF* (msec)	Comments
X	Screen		.	.	DDMMMYYYY	X:XX:XX	Normal	XX	XXX.X	XX.X	XXX.X	XXX.X	XXX.X	
	X	X	X	X.X	DDMMMYYYY	X:XX:XX	Abnormal,NCS	XX	XXX.X	XX.X	XXX.X	XXX.X	XXX.X	

Note: QTcB* = QTc corrected using Bazzet's correction, QTcF* = QTc corrected using Fridericia's correction.
NCS = Not clinically significant
Treatment A = 60 mg WTX101 on Day 1 (Fasted)
Treatment B = 60 mg WTX101 on Day 1 (Fed)
Treatment C = 20 mg omeprazole QD on the morning of Days -5 to -1 (Fasted), 20 mg omeprazole capsule at Hour -1 and 60 mg WTX101 at Hour 0 on Day 1 (Fasted)

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.9.3 Phone Participant

Subject Number	Study Period	Time Point	Date	Time	Result	Comments
X	All	First attempt	DDMMMYYYY	HH:MM	XXXXX	XXXXXXXXXXX

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM