**Supplementary data and analyses**

# A phase 1 dose-escalation study: safety, tolerability, and pharmacokinetics of FBS0701, a novel oral iron chelator for the treatment of transfusional iron overload

| Term | Definition |
|---|---|
| $AUC_{(0-24)}$ | Area under the plasma concentration-time curve over a 24-hour steady-state dosing interval |
| CL/F | Total plasma clearance uncorrected for bioavailability |
| CLr | Renal clearance |
| $C_{max}$ | Maximum plasma concentration |
| Cu | Concentration of drug in the urine |
| F | Bioavailability |
| Fe | Fraction excreted unchanged in the urine |
| h | Hour |
| LC/MS/MS | Liquid chromatography/mass spectrometry/mass spectrometry |
| LOQ | Validated lower limit of the bioanalytical method |
| Kg | kilogram |
| mg | milligram |
| mL | milliliter |
| ng | nanogram |
| PK | Pharmacokinetics |
| t | time |
| $t_{½}$ | Elimination half-life |
| $t_{max}$ | Time of maximum plasma concentration |
| UE | Amount excreted unchanged in the urine |
| Vu | Volume of urine |
| Vz/F | Volume of distribution uncorrected for bioavailability |
| λz | Elimination rate constant |

**Safety**

**Table S1. Schedule of assessments.**

| Visit Name | Screening | Enroll-ment | Start of Treatment | Patient at Home (Contact by Phone) | Clinic Visit | Clinic Visit | Last Day of Treatment Visit | | | | Follow-up Visits | | Follow-up Safety Visits | Study Termination Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Date | Days -45 to -1 | Day -5 to -2 | Day 1 | Day 2 and Day 4 and Day 5 | Day 3 | Day 6 | Day 7 Pre-dose | Day 7 15 to 180 min post dose | Day 7 4 Hr. post dose | Day 7 8 Hr. post dose | Day 8 and Day 15 | Day 9 and Day 10 | Day 21 ± 2 and Day 28 ± 2 | Day 35 ± 4 |
| Informed Consent | X | | | | | | | | | | | | | |
| Inclusion/Exclusion | X | | | | | | | | | | | | | |
| Verify Patient Eligibility | | | X | | | | | | | | | | | |
| Medical History | X | | X | | | | | | | | | | | |
| Complete PE | X | | | | | | | | X | | | | | |
| Limited PE | | | X | | X | X | | | | | X | | | |
| 12-lead ECG | X | | | | | | | | X | | | | | |
| Vital Signs (HR, BP,RR, Temp) | X | | X | | X | X | X | | X | | X | X | | |
| Height | X | | | | | | | | | | | | | |
| Weight | X | | X | | | | | | X | | | | | |
| Concomitant Medications | X | | X | X | X | X | X | | | X | X | X | X | X |
| Adverse Event Collection | | | X (post dose) | X | X | X | X | | | X | X | X | X | X |
| Hematology | X | | X | | | | | | | | X | | | |
| Complete Serum Biochemistry | X | | X | | | | | | | | X | | | |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Coagulation (PT/PTT) | X | | X | | | | | | | | X | | | |
| UA with Microscopy | X | | X | | | | | | | | X | | | |
| Serum HCG | X | | | | | | | | | | | | | |
| Urine Pregnancy Test | | | X | | | | | | | | X[c] | | | |
| 24 Urine Collection | | | | | | | | | X (0 to 4 Hr) | X (4 to 8 Hr)[a] | | | | |
| Stop Current Chelator Tx | | X | | | | | | | | | | | | |
| PK Blood Samples | | | X (pre-dose) | | X (pre-dose) | X (pre-dose) | X (pre-dose) | X[b] | X | X | X | X | | |
| FBS0701 Dosing | | | X | X (at home) | X | X | X | | | | | | | |
| Dispense FBS0701 for at-home dosing | | | X | | X | | | | | | | | | |
| Restart previous chelator therapy | | | | | | | | | | | X[d] | | | |

a) Dispense third urine container to patient to collect urine from 8 to 24 hours post-last dose.
b) PK samples to be drawn post-dose at: 15, 30, 45, 60, 90, 120 and 180 minutes.
c) Urine pregnancy test on 15 only
d) Restart patient's previous chelator on day 15 if Principal Investor deems safe

## Table S2. Patients' demographics.

| Treatment | Subject ID | Age (years) | Sex | Ethnicity | Race |
|---|---|---|---|---|---|
| FBS0701: 3 mg/kg/d | 0101 | 18 | Female | Not Hispanic or Latino | White |
| | 0501 | 18 | Female | Not Hispanic or Latino | Black or African American |
| | 0601 | 19 | Female | Not Hispanic or Latino | Other, Specify: Lebanese |
| | 0603 | 22 | Male | Not Hispanic or Latino | Black or African American |
| FBS0701: 8 mg/kg/d | 0102 | 25 | Female | Not Hispanic or Latino | Asian |
| | 0502 | 29 | Female | Not Hispanic or Latino | Asian |
| | 0604 | 40 | Female | Not Hispanic or Latino | White |
| | 0605 | 31 | Male | Not Hispanic or Latino | White |
| FBS0701: 16 mg/kg/d | 0503 | 41 | Male | Not Hispanic or Latino | Asian |
| | 0701 | 22 | Female | Not Hispanic or Latino | Asian |
| | 0702 | 18 | Male | Not Hispanic or Latino | Asian |
| | 0801 | 38 | Male | Not Hispanic or Latino | White |
| FBS0701: 32 mg/kg/d | 0504 | 34 | Female | Not Hispanic or Latino | Asian |
| | 0703 | 21 | Female | Not Hispanic or Latino | Asian |
| | 0704 | 20 | Female | Not Hispanic or Latino | Asian |
| | 0802 | 20 | Female | Not Hispanic or Latino | Black or African American |

## Table S3. Specific medical history.

| Treatment | Subject ID | Patient's Qualifying LIC (mg/g) | Cardiac Function (T2) | Does the patient have a history of hepatitis B/C? | Does the patient have a history of cholecystitis? | Does the patient have a history of adrenal insufficiency? |
|---|---|---|---|---|---|---|
| FBS0701: 3 mg/kg/d | 0101 | 1.5 | 34.5 | No | No | No |
| | 0501 | 38.7 | 33.1 | No | Yes | No |
| | 0601 | 10.2 | 37.9 | No | No | No |
| | 0603 | 4.4 | 34.8 | No | No | No |
| FBS0701: 8 mg/kg/d | 0102 | 12.9 | 37 | No | No | No |
| | 0502 | 23.3 | 18.3 | No | No | No |
| | 0604 | 2.2 | 30.8 | No | Yes | No |
| | 0605 | 31.5 | 13.3 | No | No | No |
| FBS0701: 16 mg/kg/d | 0503 | 11.4 | 14.6 | Yes | No | No |
| | 0701 | 2.9 | 35.8 | No | No | No |
| | 0702 | 17.8 | 40.1 | No | No | No |
| | 0801 | 24.3 | 12.8 | Yes | Yes | No |
| FBS0701: 32 mg/kg/d | 0504 | 16.4 | 13.4 | No | Yes | No |
| | 0703 | 21.4 | 12.4 | No | No | No |
| | 0704 | 23.6 | 38 | No | No | No |
| | 0802 | 36.4 | 37.3 | No | No | No |

**Table S4. All adverse events by dose.**

| Patient ID | Adverse Event | Intensity | Outcome | Causality | SAE | Dose of FBS0701 in mg/kg |
|---|---|---|---|---|---|---|
| 101 | Transfusion Related Reaction | Moderate | Resolved | Not Related | No | 3 |
| 101 | Otitis Media | Mild | Resolved | Not Related | No | 3 |
| 501 | Insect Bite | Mild | Resolved | Not Related | No | 3 |
| 501 | Sickle Cell Crisis | Moderate | Resolved | Not Related | Yes | 3 |
| 501 | Low Back Pain | Mild | Resolved | Not Related | No | 3 |
| 601 | Inflammation at Cannula Site | Mild | Resolved | Not Related | No | 3 |
| 603 | Upper Respiratory Tract Infection | Moderate | Resolved | Not Related | No | 3 |
| 603 | Flatulence | Mild | Resolved | Possibly Related | No | 3 |
| 603 | Headache | Mild | Resolved | Possibly Related | No | 3 |
| 102 | Upper respiratory tract infection | Mild | Resolved | Not Related | No | 8 |
| 502 | Left ankle sprain | Moderate | Resolved | Not related | No | 8 |
| 604 | [No AEs] | | | | | 8 |
| 605 | Abdominal Warmth | Mild | Resolved | Possibly Related | No | 8 |
| 701 | Headache | Mild | Resolved | Not Related | No | 16 |
| 701 | Urine Color Change | Mild | Resolved | Probably Related | No | 16 |
| 701 | Febrile Viral Illness | Mild | Resolved | Not Related | No | 16 |
| 702 | Urine Color Change | Mild | Resolved | Probably Related | No | 16 |
| 503 | Light headedness | Mild | Resolved | Possibly Related | No | 16 |
| 503 | Headache | Moderate | Resolved | Not Related | No | 16 |
| 801 | Right Shoulder and Back Pain | Mild | Resolved | Not Related | No | 16 |
| 801 | 5$^{th}$ Digit abrasion | Mild | Resolved | Not Related | No | 16 |
| 801 | Blood in Urine | Mild | Resolved | Probably Related | No | 16 |
| 801 | Sciatic Nerve Pain | Mild | Resolved | Not Related | No | 16 |

| Patient ID | Adverse Event | Intensity | Outcome | Causality | SAE | Dose of FBS0701 in mg/kg |
|---|---|---|---|---|---|---|
| 704 | Urine color change | Mild | Resolved | Probably Related | No | 32 |
| 704 | Headache | Mild | Resolved | Possibly Related | No | 32 |
| 802 | Bright colored urine | Mild | Resolved | Possibly Related | No | 32 |
| 802 | Pruritus | Mild | Resolved | Possibly Related | No | 32 |
| 802 | QTc Change | Mild | Resolved | Possibly Related | No | 32 |
| 802 | Flatulence | Mild | Resolved | Possibly Related | No | 32 |
| 802 | Gas pains/Flatulence | Mild | Resolved | Possibly Related | No | 32 |
| 802 | Superficial venous thrombus | Mild | Resolved | Not Related | No | 32 |
| 802 | Tachycardia | Mild | Resolved | Possibly Related | No | 32 |
| 504 | [No AEs] | | | | | 32 |

## Pharmacokinetic and statistical methods

### *Pharmacokinetic analyses*

All pharmacokinetic calculations and generation of graphs of individual patients' concentration *versus* time were done using SAS® for Windows® Version 9.1.3 under Windows XP Professional. Graphs of mean plasma concentration and other in-text graphs were prepared using SigmaPlot® for Windows® Version 11.

On day 7, the maximum plasma concentration ($C_{max}$) and time to $C_{max}$ ($T_{max}$) were taken directly from the data. The elimination rate constant, $\lambda z$, 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 linear regression of the natural logarithm of the terminal plasma concentrations against time; at least three terminal plasma concentration time points, beginning with the final concentration ≥ LOQ, were selected for the determination of λz and the regression had to have a coefficient of determination ($r^2$) ≥ 0.9000. The range of data used for each patient was determined by visual inspection of a semi-logarithmic plot of concentration *versus* time. Elimination half-life (t½) was calculated according to the following equation:

$$t? = \frac{0.693}{\lambda z}$$

Area under the curve over the 24-hour dosing interval [$AUC_{(0\text{-}24)}$] was calculated using the linear trapezoidal method.

Oral clearance (CL/F) and volume of distribution (Vz/F), uncorrected for bioavailability (F) were calculated using the following formulae:

$$CL/F = \frac{Dose}{AUC(0-24)} \text{ and } Vz/F = \frac{Dose}{\lambda z \times AUC(0-24)},$$

respectively.

For each urine collection interval, the amount of FBS0701 excreted (Ue) was calculated from the concentration (Cu) and volume (Vu), i.e.

$$Ue = Cu \times Vu$$

and the total amount excreted over the 24-hour steady-state period was calculated by summing the amounts from the individual intervals and was expressed as both milligrams (Ue) and percent of dose (Fe).

Renal clearance (CLr) was calculated for the 24-hour steady-state period according to

$$CLr = \frac{Ue(0-24)}{AUC(0-24)}$$

where Ue and AUC are as previously defined.

***Protocol deviations***

The day 15 blood sample (336 h) for Patient #802 was collected on day 17 (384 h). Although this sample was included in all pharmacokinetic analyses, it was excluded from the calculation of descriptive statistics for plasma concentrations (Appendix IV).

***Detailed analysis***

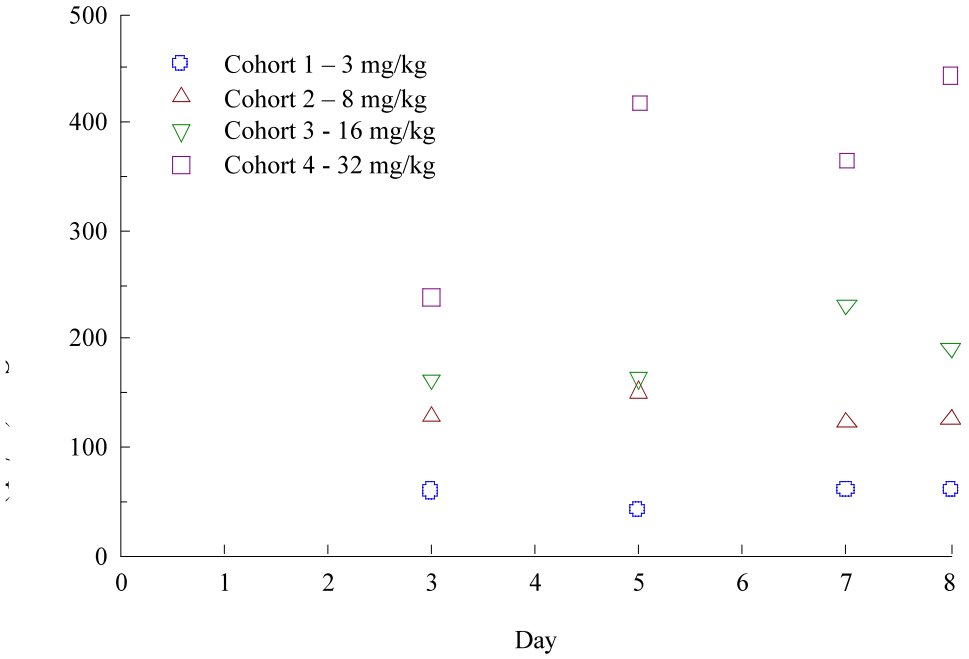
The individual patients' dosing times are listed in Appendix I. Individual patients' FBS0701 plasma concentrations, actual sampling times, and mean plasma concentrations are listed in Appendix II, Appendix III, and Appendix IV, respectively. The individual patients' FBS0701 urinary excretion data are contained in Appendix V. Appendix VI and Appendix VII contain the individual patients' pharmacokinetic parameters and the associated descriptive statistics. The statistical analysis of the fit of the power model to $C_{max}$ and $AUC_{(0\text{-}24)}$ *versus* total dose is shown in Appendix VIII. The individual patients' plots of plasma concentration *versus* time on linear and semi-logarithmic axes, respectively; are in Appendix IX and Appendix X; the latter contains line segments indicating the range of data used to estimate λz.

***Attainment of steady-state***

Taking into account the small number of patients per cohort, with the exception of cohort 4 (32 mg/kg/day), the mean pre-dose plasma concentrations were relatively constant from day 3 through day 8 (*Online Supplementary Figure S1*), suggesting that steady-state had been reached by day 3, consistent with the mean t½ (16.2 to 21.3 h; *Online Supplementary Table S5*) and the 24-hour dosing interval.

Patient #703 had pre-dose plasma concentrations that were substantially higher than the other three patients in cohort 4 (Appendix II) and may account for the increased variability within this group.

Figure S1: Mean pre-dose plasma concentrations of FBS0701 on Days 3, 5, and 7 and 24 hours after the last dose on Day 7 (Day 8) during oral administration of 3, 8, 16, or 32 mg/kg/day × 7 days to patients with transfusional iron overload.



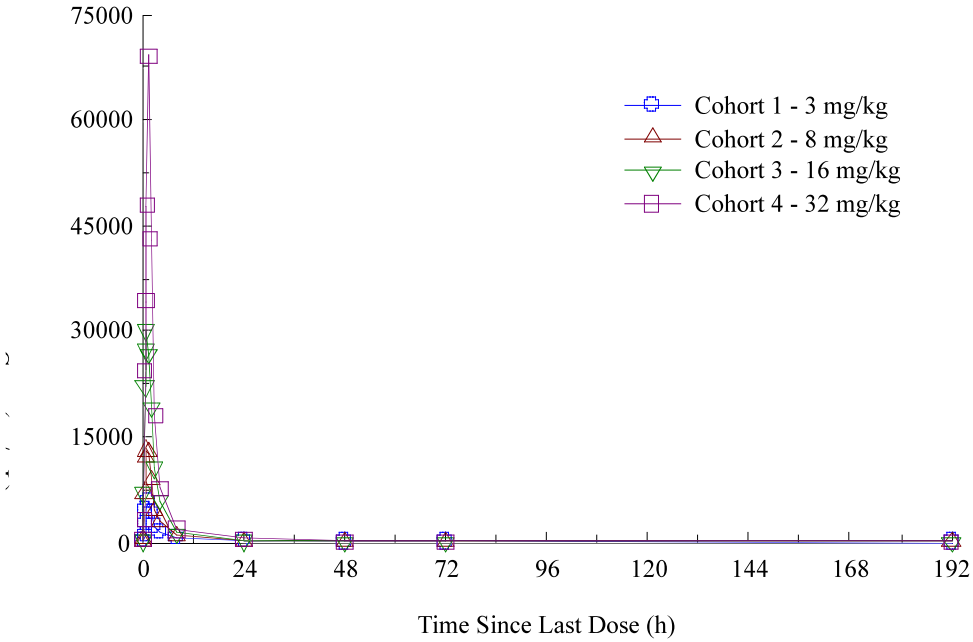

Source: Appendix IV.

***Pharmacokinetics***

The mean plasma FBS0701 concentrations after the last dose on day 7 are illustrated on linear axes in *Online Supplementary Figure S2 and Figure S3* (initial 24 hours) and in *Online Supplementary Figure S4* (semi-logarithmic axes). Plasma concentrations increased in a dose-related manner (*Online Supplementary Figure S3*) and, as illustrated in *Online Supplementary Figure S4*, decay at essentially the same rate after all four doses, demonstrating linear pharmacokinetics. Mean values for $C_{max}$ and $AUC_{(0\text{-}24)}$ also increased in a dose-proportional manner (*Online Supplementary Table S5*) and log-log plots of the individual $C_{max}$ (*Online Supplementary Figure S5*) and $AUC_{(0\text{-}24)}$ (*Online Supplementary Figure S6*) *versus* dose were reasonably linear with slopes whose

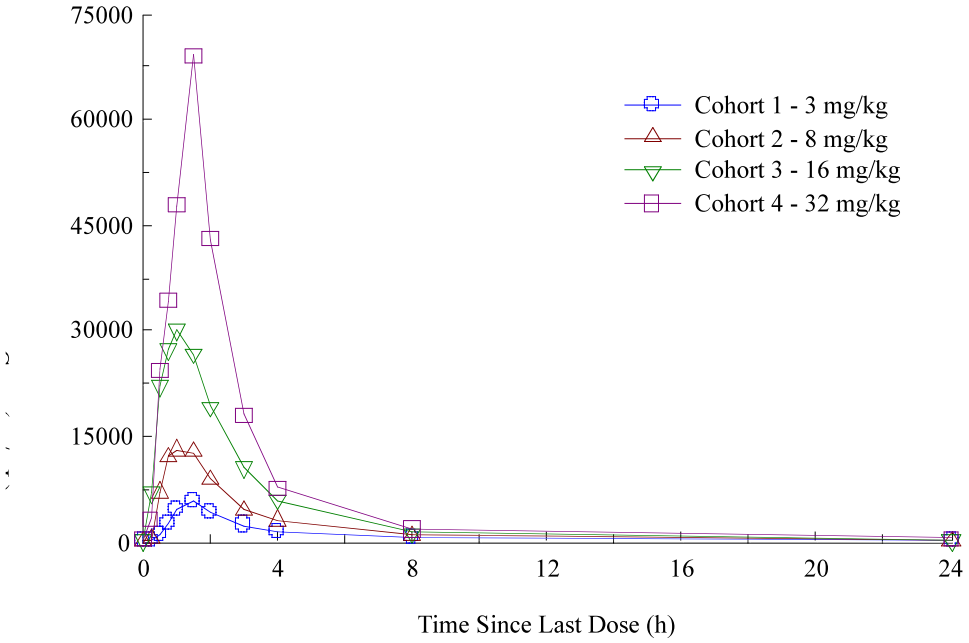
approximate 95% confidence intervals included 1.0 (Appendix VIII), providing further evidence of linear pharmacokinetics. The median values for $T_{max}$ ranged from 1.00 to 1.49 h and were not dependent on dose (*Online Supplementary Table S5*). There were no dose-related trends in either CL/F or Vz/F and the mean elimination half-life ($t_{½}$) ranged from 16.2 h to 21.3 h and was independent of dose (*Online Supplementary Table S5*).

Figure S2: Mean plasma concentrations of FBS0701 on day 7 after oral administration of 3, 8, 16, or 32 mg/kg/day for 7 days to patients with transfusional iron overload — linear axes.



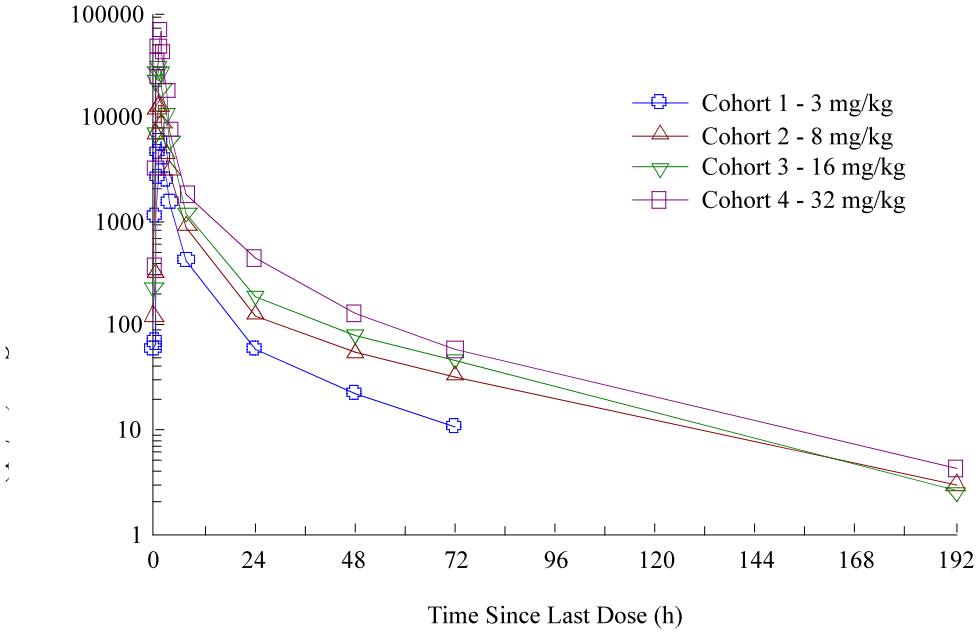

Source: Appendix IV.

Figure S3: Mean plasma concentrations of FBS0701 on day 7 after oral administration of 3, 8, 16, or 32 mg/kg/day for 7 days to patients with transfusional iron overload — linear axes — initial 24 hours.




Source: Appendix IV.

Figure S4: Mean plasma concentrations of FBS0701 on day 7 after oral administration of 3, 8, 16, or 32 mg/kg/day for 7 days to patients with transfusional iron overload — semi-logarithmic axes.




Source: Appendix IV.

Table S5: Summary of pharmacokinetic parameters for FBS0701 on day 7 after oral administration of 3, 8, 16, or 32 mg/kg/day for 7 days to patients with transfusional iron overload.

| | Dose | | | |
|---|---|---|---|---|
| Parameter* | 3 mg/kg/day | 8 mg/kg/day | 16 mg/kg/day | 32 mg/kg/day |
| Cmax (ng/mL) | 5,910 ± 2,298 (4) | 15,000 ± 4,439 (4) | 38,225 ± 3,947 (4) | 68,250 ± 27,519 (4) |
| Tmax (h) | 1.31 (4) | 1.18 (4) | 1.00 (4) | 1.49 (4) |
| AUC(0-24) ($h^2$ ng/mL) | 19,476 ± 11,327 (4) | 44,916 ± 30,751 (4) | 92,261 ± 36,560 (4) | 157,577 ± 43,484 (4) |
| $\lambda_z$ ($h^{-1}$) | 0.0655 ± 0.0606 (4) | 0.0424 ± 0.0249 (4) | 0.0421 ± 0.0246 (4) | 0.0381 ± 0.0091 (2) |
| t1/2 (h) | 16.2 ± 8.32 (4) | 20.9 ± 11.3 (4) | 21.3 ± 11.8 (4) | 18.7 ± 4.48 (2) |
| CL/F (mL/min) | 162 ± 85.0 (4) | 225 ± 142 (4) | 206 ± 78.4 (4) | 172 ± 60.1 (4) |
| Vz/F (L) | 185 ± 84.1 (4) | 311 ± 137 (4) | 339 ± 166 (4) | 214 ± 2.94 (2) |
| Ue(0-24) (mg) | 66.1 ± 24.0 (4) | 201 ± 68.1 (4) | 402 ± 103 (4) | 641 ± 208 (4) |
| Fe(0-24) (% Dose) | 44.0 ± 16.0 (4) | 47.4 ± 13.8 (4) | 39.2 ± 5.86 (4) | 43.1 ± 15.8 (4) |
| CLr (mL/min) | 75.2 ± 46.8 (4) | 105 ± 62.9 (4) | 83.2 ± 36.5 (4) | 73.6 ± 37.8 (4) |

*Arithmetic mean ± standard deviation (N) except Tmax for which the median (N) is reported.

Source: Appendix IX.

Figure S5: Relationships between individual patients' $C_{max}$ and total dose of FBS0701 on day 7 during oral administration of 3, 8, 16, or 32 mg/kg/day to patients with transfusional iron overload.

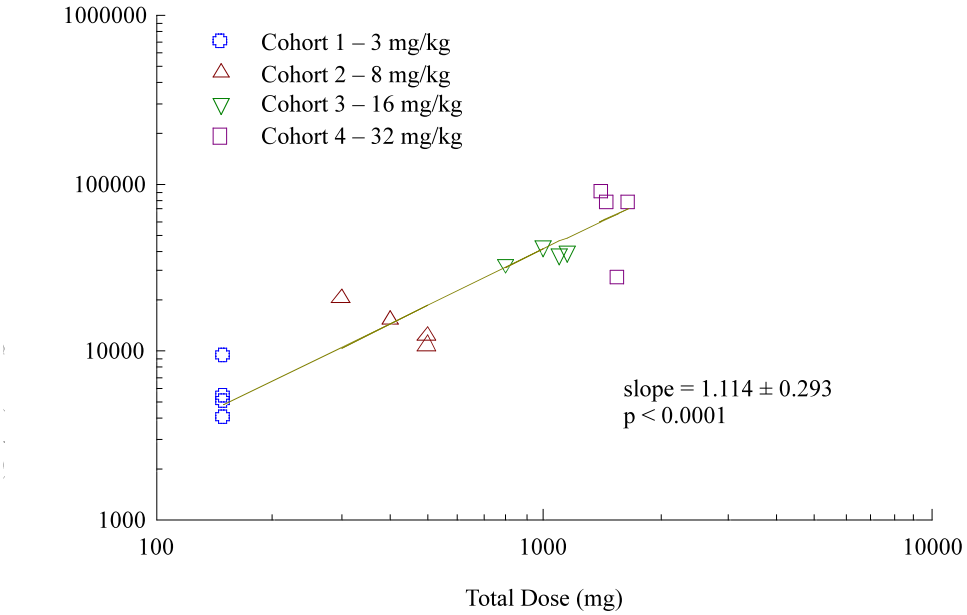
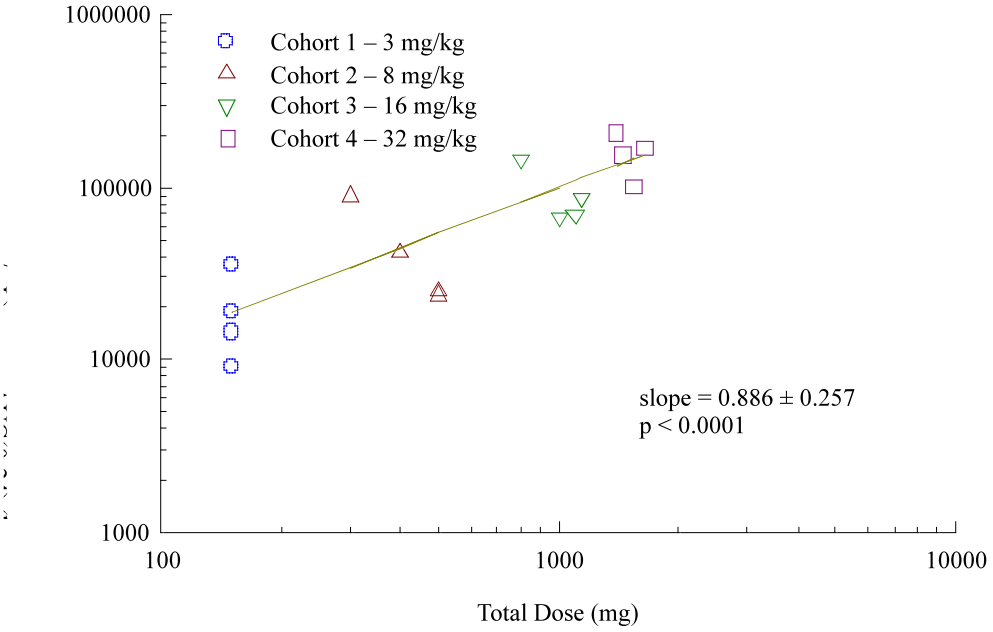
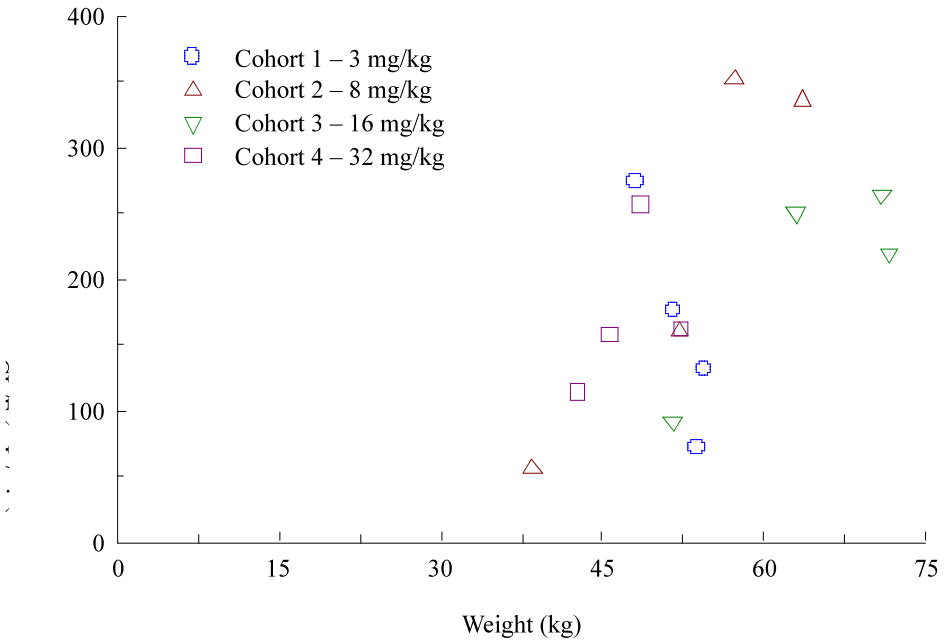



Figure S6: Relationships between individual patients' $AUC_{(0-24)}$ and total dose of FBS0701 on day 7 during oral administration of 3, 8, 16, or 32 mg/kg/day to patients with transfusional iron overload.



As illustrated in *Onine Supplementary Figure S7*, CL/F appears to be directly related to body weight, suggesting that weight-based dosing may be appropriate for FBS0701. However, this is based on a small number of patients and the need for a weight-based *versus* a fixed dose must be confirmed in a larger sample size.

Figure S7: Relationship between individual patients' FBS0701 CL/F and body weight after oral administration of 3, 8, 16, or 32 mg/kg/day to patients with transfusional iron overload.




Consistent with linear pharmacokinetics, the urinary recovery of FBS0701 was comparable across the four cohorts, with mean recovery ranging from 39.2% to 47.4% of the dose (*Online Supplementary Table S5*). The mean renal clearance ranged from 73.6 to 105 mL/min (*Online Supplementary Table S5*). As the protein binding of FBS0701 is 85%, filtration clearance, estimated as the unbound fraction, 0.15, times the glomerular filtration rate, ~120 mL/min, would be ~18 mL/min. As CLr is ~5-fold greater than the filtration clearance, active tubular secretion is likely a substantial component of the renal excretion of FBS0701.

***Assessment of the linearity of renal clearance***

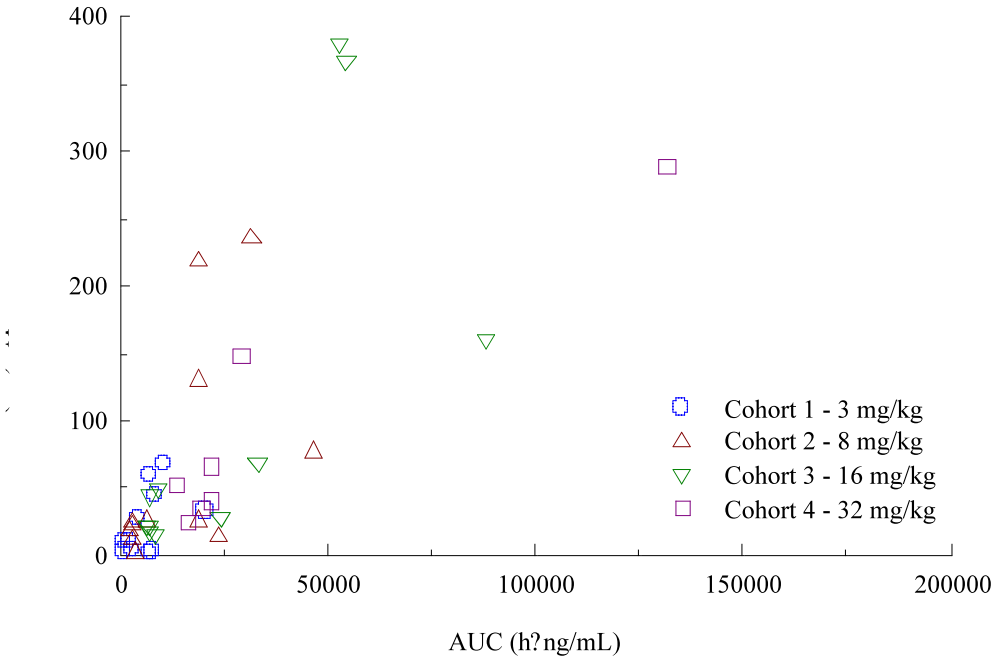
As indicated above, the mean CLr of FBS0701 ranged from 73.6 to 105 mL/min, ~5-fold greater than filtration clearance, indicating that active tubular secretion is likely a substantial component of the renal excretion of FBS0701. Active tubular secretion is an excretion pathway that can potentially be saturated; however, if true, this would not affect the absolute recovery, which is independent of dose (*Online Supplementary Table S5*).

The amount excreted within a collection interval (UE) and the area under the curve for that interval (AUC) are related via

$$UE = CLr \times AUC$$

and thus a plot of UE *versus* AUC should be linear if there is no saturation of renal clearance. As shown in *Online Supplementary Figure S8*, within the limits of the small number of patients per cohort and the variability intrinsic to estimating urinary excretion, there is a reasonably linear relationship between UE and AUC up to an AUC of ~150,000 h×ng/mL, indicating no apparent trends toward saturation.

Figure S8: Individual patients' amount excreted *versus* area under the curve for individual urine collection intervals.



Appendix I
Individual Patient Actual Dosing Times (h)

| Cohort | Patient | Body Weight (kg) | Total Dose (mg) | Actual Dose (mg/kg) | Scheduled Dose Time (h)* | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 |
| 1 | 101 | 53.8 | 150 | 2.79 | 0.00 | 23.00 | 47.63 | 71.00 | 95.00 | 120.17 | 142.87 |
| | 501 | 48.1 | 150 | 3.12 | 0.00 | 24.07 | 49.00 | 72.75 | 94.75 | 119.58 | 143.60 |
| | 601 | 51.7 | 150 | 2.90 | 0.00 | 24.00 | 48.00 | 72.00 | 96.00 | 120.00 | 144.02 |
| | 603 | 54.4 | 150 | 2.76 | 0.00 | 24.00 | 48.00 | 72.00 | 96.00 | 120.00 | 144.00 |
| 2 | 102 | 52.1 | 400 | 7.68 | 0.00 | 23.83 | 48.25 | 71.92 | 95.83 | 119.98 | 142.08 |
| | 502 | 63.5 | 500 | 7.87 | 0.00 | 23.05 | 47.63 | 70.88 | 95.22 | 119.80 | 144.18 |
| | 604 | 38.5 | 300 | 7.79 | 0.00 | 24.00 | 47.77 | 71.77 | 95.77 | 119.77 | 143.77 |
| | 605 | 57.2 | 500 | 8.74 | 0.00 | 24.00 | 47.75 | 71.75 | 95.75 | 119.75 | 143.75 |
| 3 | 503 | 62.9 | 1,000 | 15.9 | 0.00 | 22.08 | 47.92 | 70.50 | 94.50 | 119.83 | 143.33 |
| | 701 | 51.5 | 800 | 15.5 | 0.00 | 22.83 | 47.58 | 70.50 | 94.92 | 120.00 | 142.50 |
| | 702 | 70.9 | 1,100 | 15.5 | 0.00 | 22.50 | 46.83 | 70.50 | 94.00 | 119.12 | 142.75 |
| | 801 | 71.6 | 1,150 | 16.1 | 0.00 | 24.05 | 47.82 | 71.95 | 95.95 | 121.02 | 144.08 |
| 4 | 504 | 52.3 | 1,650 | 31.5 | 0.00 | 24.08 | 48.75 | 72.58 | 96.67 | 120.67 | 144.00 |
| | 703 | 45.7 | 1,450 | 31.7 | 0.00 | 23.05 | 48.22 | 71.55 | 95.55 | 120.38 | 143.55 |
| | 704 | 42.7 | 1,400 | 32.8 | 0.00 | 23.30 | 48.13 | 71.30 | 95.30 | 119.88 | 142.80 |
| | 802 | 48.5 | 1,550 | 32.0 | 0.00 | 23.93 | 47.80 | 72.00 | 96.03 | 119.80 | 145.10 |

*Time since the first dose on Day 1

Appendix II
Individual Patient Plasma Concentrations (ng/mL)

| | | Scheduled Time (h)* | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Day 3 | Day 5 | Day 7 | | | | | | | | | | Day 8 | Day 9 | Day 10 | Day 15 |
| Cohort | Patient | 0 | 48 | 96 | 144 | 144.25 | 144.5 | 144.75 | 145 | 145.5 | 146 | 147 | 148 | 152 | 168 | 192 | 216 | 336 |
| 1 | 101 | 0.0 | 79.2 | 27.4 | 72.0 | 80.2 | 774 | 3,200 | 7,030 | 9,250 | 7,770 | 4,890 | 3,180 | 781 | 83.3 | 37.1 | 20.3 | . |
| | 501 | 0.0 | 30.3 | 14.4 | 10.4 | 17.7 | 2,640 | 4,010 | 3,830 | 2,890 | 1,620 | 1,070 | 454 | 104 | 14.1 | 0.0 | 0.0 | 0.0 |
| | 601 | 0.0 | 70.0 | 65.9 | 96.8 | 113.0 | 669 | 1,860 | 4,170 | 5,040 | 2,720 | 1,350 | 926 | 316 | 85.3 | 34.6 | 15.9 | 0.0 |
| | 603 | 0.0 | 53.9 | 58.0 | 57.1 | 61.6 | 413 | 1,440 | 3,150 | 5,340 | 4,330 | 2,260 | 1,590 | 486 | 52.0 | 17.2 | 7.1 | 0.0 |
| 2 | 102 | 0.0 | 51.6 | 48.7 | 71.0 | 381.0 | 2,900 | 5,940 | 10,300 | 15,600 | 13,600 | 5,820 | 2,770 | 359 | 50.2 | 20.0 | 11.5 | 0.0 |
| | 502 | 0.0 | 38.2 | 58.8 | 55.8 | 231.0 | 11,400 | 12,400 | 10,900 | 6,930 | 3,370 | 1,690 | 1,310 | 310 | 66.2 | 13.4 | 0.0 | 0.0 |
| | 604 | 0.0 | 337.0 | 443.0 | 314.0 | 452.0 | 9,210 | 20,500 | 21,000 | 17,300 | 13,000 | 8,790 | 7,090 | 2,600 | 335.0 | 172.0 | 113.0 | 11.8 |
| | 605 | 0.0 | 83.9 | 49.6 | 52.4 | 228.0 | 4,630 | 9,380 | 9,610 | 11,000 | 5,210 | 1,610 | 894 | 294 | 49.6 | 12.6 | 6.5 | 0.0 |
| 3 | 503 | 0.0 | 187.0 | 168.0 | 144.0 | 13,500.0 | 42,500 | 31,000 | 22,400 | 16,900 | 10,400 | 4,480 | 2,940 | 669 | 156.0 | 63.7 | 44.4 | 0.0 |
| | 701 | 0.0 | 225.0 | 226.0 | 306.0 | 461.0 | 1,580 | 15,900 | 30,900 | 33,000 | 32,100 | 24,100 | 14,000 | 2,690 | 266.0 | 170.0 | 125.0 | 10.1 |
| | 702 | 0.0 | 93.7 | 143.0 | 264.0 | 13,300.0 | 38,100 | 34,200 | 29,800 | 17,700 | 10,200 | 4,190 | 2,590 | 850 | 190.0 | 60.2 | 18.6 | 0.0 |
| | 801 | 0.0 | 142.0 | 114.0 | 213.0 | 218.0 | 5,930 | 28,200 | 37,400 | 39,300 | 24,100 | 9,570 | 3,980 | 645 | 154.0 | 32.9 | 0.0 | 0.0 |
| 4 | 504 | 0.0 | 237.0 | 431.0 | 289.0 | 544.0 | 10,600 | 21,700 | 53,600 | 77,300 | 50,500 | 21,100 | 9,420 | 1,570 | 409.0 | 129.0 | 46.2 | 12.7 |
| | 703 | 0.0 | 255.0 | 726.0 | 727.0 | 11,000.0 | 61,600 | 77,400 | 72,600 | 39,500 | 25,200 | 9,570 | 5,010 | 1,830 | 913.0 | 224.0 | 109.0 | 0.0 |
| | 704 | 0.0 | 392.0 | 346.0 | 326.0 | 1,280.0 | 13,000 | 18,500 | 37,500 | 90,300 | 68,600 | 31,500 | 12,500 | 2,080 | 370.0 | 147.0 | 81.4 | 0.0 |
| | 802 | 0.0 | 68.3 | 167.0 | 118.0 | 192.0 | 12,400 | 19,500 | 27,700 | . | 28,000 | 9,850 | 3,550 | . | 80.0 | 26.0 | 0.0 | 20.0 |

Assay LOQ = 5 ng/mL
(. = no sample analyzed and/or reported)
*Time since the first dose on Day 1

Appendix III
Individual Patient Blood Sampling Times (h)

| | | Scheduled Time (h)* | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Day 3 | Day 5 | Day 7 | | | | | | | | | | Day 8 | Day 9 | Day 10 | Day 15 |
| Cohort | Patient | 0 | 48 | 96 | 144 | 144.25 | 144.5 | 144.75 | 145 | 145.5 | 146 | 147 | 148 | 152 | 168 | 192 | 216 | 336 |
| 1 | 101 | -1.00 | 47.00 | 95.33 | 142.83 | 143.12 | 143.37 | 143.62 | 143.87 | 144.37 | 144.87 | 145.87 | 146.87 | 150.87 | 166.67 | 190.75 | 214.92 | . |
| | 501 | -0.03 | 48.97 | 95.50 | 143.58 | 143.85 | 144.08 | 144.33 | 144.62 | 145.08 | 145.58 | 146.62 | 147.60 | 151.58 | 168.00 | 192.50 | 216.28 | 335.58 |
| | 601 | -0.35 | 47.38 | 95.45 | 143.52 | 144.27 | 144.52 | 144.77 | 145.02 | 145.52 | 146.02 | 147.02 | 148.02 | 152.00 | 168.02 | 192.00 | 216.02 | 336.07 |
| | 603 | -0.22 | 47.53 | 95.82 | 143.87 | 144.25 | 144.50 | 144.75 | 145.00 | 145.50 | 146.00 | 147.00 | 148.00 | 152.00 | 168.00 | 192.00 | 216.00 | 336.00 |
| 2 | 102 | -0.25 | 48.05 | 95.92 | 141.83 | 142.33 | 142.58 | 142.83 | 143.08 | 143.58 | 144.13 | 145.08 | 146.08 | 150.13 | 168.17 | 192.42 | 216.08 | 335.83 |
| | 502 | -0.03 | 47.55 | 95.72 | 144.13 | 144.43 | 144.68 | 144.92 | 145.18 | 145.68 | 146.20 | 147.18 | 148.38 | 152.18 | 168.22 | 192.47 | 216.05 | 335.47 |
| | 604 | -0.33 | 47.57 | 95.50 | 143.23 | 144.02 | 144.27 | 144.52 | 144.77 | 145.27 | 145.77 | 146.77 | 147.83 | 151.77 | 167.85 | 191.77 | 215.77 | 335.83 |
| | 605 | -0.43 | 47.45 | 95.37 | 143.30 | 144.00 | 144.25 | 144.50 | 144.75 | 145.25 | 145.75 | 146.75 | 147.75 | 151.75 | 167.75 | 191.75 | 215.75 | 335.75 |
| 3 | 503 | -0.58 | 47.83 | 119.78 | 143.30 | 143.58 | 143.83 | 144.08 | 144.35 | 144.83 | 145.37 | 146.33 | 147.32 | 151.33 | 167.88 | 191.67 | 215.58 | 335.80 |
| | 701 | -0.17 | 47.17 | 119.28 | 142.28 | 142.75 | 143.02 | 143.27 | 143.50 | 144.00 | 144.50 | 145.52 | 146.53 | 150.50 | 166.78 | 190.88 | 215.03 | 335.33 |
| | 702 | -0.08 | 46.62 | 118.58 | 142.67 | 143.02 | 143.25 | 143.52 | 143.75 | 144.23 | 144.78 | 145.75 | 146.77 | 150.75 | 166.73 | 190.72 | 214.73 | 334.53 |
| | 801 | -0.10 | 47.78 | 121.00 | 143.98 | 144.35 | 144.55 | 144.82 | 145.07 | 145.60 | 146.05 | 147.05 | 148.07 | 152.05 | 167.73 | 191.72 | 215.77 | 334.48 |
| 4 | 504 | -0.17 | 48.67 | 120.25 | 143.92 | 144.27 | 144.50 | 144.75 | 145.00 | 145.50 | 146.03 | 147.02 | 148.00 | 152.00 | 168.50 | 192.52 | 216.17 | 336.42 |
| | 703 | -0.28 | 47.63 | 119.88 | 143.05 | 143.78 | 144.05 | 144.32 | 144.55 | 145.08 | 145.55 | 146.73 | 147.55 | 151.53 | 167.47 | 190.93 | 215.13 | 311.13 |
| | 704 | -0.17 | 47.43 | 119.22 | 142.35 | 143.05 | 143.28 | 143.57 | 143.83 | 144.32 | 144.82 | 145.83 | 146.80 | 150.80 | 166.77 | 190.72 | 214.63 | 334.63 |
| | 802 | -0.08 | 47.77 | 119.75 | 145.02 | 145.37 | 145.58 | 145.87 | 146.13 | . | 147.27 | 148.02 | 149.10 | . | 168.68 | 191.95 | 215.77 | 390.80 |

(. = no sample analyzed and/or reported)
*Time since the first dose on Day 1

Appendix IV
Mean ± Standard Deviation Plasma Concentrations*

| Scheduled Time (h)* | Concentration (ng/mL) Cohort 1 (3 mg/kg) | Cohort 2 (8 mg/kg) | Cohort 3 (16 mg/kg) | Cohort 4 (32 mg/kg) |
|---|---|---|---|---|
| 0.00 | 0.00 ± 0.00 (4) | 0.00 ± 0.00 (4) | 0.00 ± 0.00 (4) | 0.00 ± 0.00 (4) |
| 48.00 | 58.35 ± 21.42 (4) | 127.68 ± 140.86 (4) | 161.93 ± 56.74 (4) | 238.08 ± 132.67 (4) |
| 96.00 | 41.43 ± 24.50 (4) | 150.03 ± 195.37 (4) | 162.75 ± 47.59 (4) | 417.50 ± 233.25 (4) |
| 144.00 | 59.08 ± 36.35 (4) | 123.30 ± 127.39 (4) | 231.75 ± 69.77 (4) | 365.00 ± 257.78 (4) |
| 144.25 | 68.13 ± 39.77 (4) | 323.00 ± 111.79 (4) | 6,869.75 ± 7,541.58 (4) | 3,254.00 ± 5,183.86 (4) |
| 144.50 | 1,124.00 ± 1,021.98 (4) | 7,035.00 ± 3,944.03 (4) | 22,027.50 ± 21,249.93 (4) | 24,400.00 ± 24,820.96 (4) |
| 144.75 | 2,627.50 ± 1,188.60 (4) | 12,055.00 ± 6,217.87 (4) | 27,325.00 ± 8,001.41 (4) | 34,275.00 ± 28,781.06 (4) |
| 145.00 | 4,545.00 ± 1,710.08 (4) | 12,952.50 ± 5,390.83 (4) | 30,125.00 ± 6,145.66 (4) | 47,850.00 ± 19,653.41 (4) |
| 145.50 | 5,630.00 ± 2,648.53 (4) | 12,707.50 ± 4,681.62 (4) | 26,725.00 ± 11,187.60 (4) | 69,033.33 ± 26,389.64 (3) |
| 146.00 | 4,110.00 ± 2,681.80 (4) | 8,795.00 ± 5,261.59 (4) | 19,200.00 ± 10,783.63 (4) | 43,075.00 ± 20,440.38 (4) |
| 147.00 | 2,392.50 ± 1,740.77 (4) | 4,477.50 ± 3,482.94 (4) | 10,585.00 ± 9,342.60 (4) | 18,005.00 ± 10,477.71 (4) |
| 148.00 | 1,537.50 ± 1,190.02 (4) | 3,016.00 ± 2,832.63 (4) | 5,877.50 ± 5,447.08 (4) | 7,620.00 ± 4,100.06 (4) |
| 152.00 | 421.75 ± 285.97 (4) | 890.75 ± 1,139.84 (4) | 1,213.50 ± 988.58 (4) | 1,826.67 ± 255.02 (3) |
| 168.00 | 58.68 ± 33.40 (4) | 125.25 ± 140.04 (4) | 191.50 ± 52.34 (4) | 443.00 ± 346.00 (4) |
| 192.00 | 22.23 ± 17.26 (4) | 54.50 ± 78.40 (4) | 81.70 ± 60.46 (4) | 131.50 ± 81.51 (4) |
| 216.00 | 10.82 ± 9.07 (4) | 32.76 ± 53.70 (4) | 47.00 ± 55.09 (4) | 59.15 ± 47.07 (4) |
| 336.00 | 0.00 ± 0.00 (3) | 2.95 ± 5.90 (4) | 2.53 ± 5.05 (4) | 4.23 ± 7.33 (3) |

*Arithmetic means and standard deviations (N). Values < LOQ were set equal to 0.
*Time since the first dose on Day 1
The 336 h sample for Patient #802 was collected 48 hours late and is not included in the means.

Appendix V
Individual Patient Urinary Excretion Data

| Cohort | Patient | Time Since First Dose (h) | Sample Collection — Start Date | Start Time | End Time* | Sample Data — Start Time§ | End Time§ | Duration (h) | Conc (ng/mL) | Volume (mL) | Amount (mg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 101 | 148 | 12/15/2009 | 8:25 | 14:20 | 140.92 | 146.83 | 3.97 | 131,000 | 250 | 32.75 |
| | | 152 | 12/15/2009 | 14:20 | 18:20 | 146.83 | 150.83 | 7.97 | 53,200 | 55 | 2.93 |
| | | 168 | 12/15/2009 | 18:20 | 9:30 | 150.83 | 166.00 | 23.13 | 7,220 | 350 | 2.53 |
| | 501 | 148 | 12/15/2009 | 9:45 | 13:55 | 143.50 | 147.67 | 4.07 | 330,000 | 180 | 59.40 |
| | | 152 | 12/15/2009 | 13:55 | 17:55 | 147.67 | 151.67 | 8.07 | 35,800 | 280 | 10.02 |
| | | 168 | 12/15/2009 | 17:55 | 9:40 | 151.67 | 167.42 | 23.82 | 3,530 | 860 | 3.04 |
| | 601 | 148 | 12/06/2009 | 8:14 | 11:55 | 143.98 | 147.67 | 3.65 | 43,100 | 1,022 | 44.05 |
| | | 152 | 12/06/2009 | 11:55 | 16:08 | 147.67 | 151.88 | 7.87 | 43,000 | 233 | 10.02 |
| | | 168 | 12/06/2009 | 16:08 | 8:05 | 151.88 | 167.83 | 23.82 | 11,800 | 361 | 4.26 |
| | 603 | 148 | 12/08/2009 | 7:43 | 11:39 | 143.95 | 147.88 | 3.88 | 67,700 | 1,004 | 67.97 |
| | | 152 | 12/08/2009 | . | . | . | . | . | . | . | . |
| | | 168 | 12/08/2009 | 11:39 | 7:40 | 147.88 | 167.90 | 23.90 | 19,000 | 1,434 | 27.25 |

(. = no sample analyzed and/or reported)
*End Time for the 8-24 hour collection may occur on the next calendar day
§Time since the first dose on Day 1
Patient #603 did not produce any urine between 4 and 8 hours.

Appendix V
Individual Patient Urinary Excretion Data

| Cohort | Patient | Time Since First Dose (h) | Sample Collection — Start Date | Start Time | End Time* | Sample Data — Start Time§ | End Time§ | Duration (h) | Conc (ng/mL) | Volume (mL) | Amount (mg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | 102 | 148 | 02/02/2010 | 8:45 | 12:46 | 142.08 | 146.10 | 4.02 | 262,000 | 900 | 235.80 |
| | | 152 | 02/02/2010 | 12:46 | 16:46 | 146.10 | 150.10 | 8.02 | 126,000 | 200 | 25.20 |
| | | 168 | 02/02/2010 | 16:46 | 7:45 | 150.10 | 165.08 | 23.00 | 11,500 | 200 | 2.30 |
| | 502 | 148 | 01/19/2010 | 10:10 | 14:32 | 144.05 | 148.42 | 4.23 | 683,000 | 190 | 129.77 |
| | | 152 | 01/19/2010 | 14:32 | 18:35 | 148.42 | 152.47 | 8.28 | 111,000 | 220 | 24.42 |
| | | 168 | 01/19/2010 | 18:35 | 10:30 | 152.47 | 168.38 | 24.20 | 14,600 | 1,500 | 21.90 |
| | 604 | 148 | 01/10/2010 | 7:30 | 11:33 | 143.67 | 147.72 | 3.95 | 108,000 | 712 | 76.90 |
| | | 152 | 01/10/2010 | 11:33 | 15:30 | 147.72 | 151.67 | 7.90 | 63,800 | 395 | 25.20 |
| | | 168 | 01/10/2010 | 15:30 | 7:30 | 151.67 | 167.67 | 23.90 | 18,700 | 760 | 14.21 |
| | 605 | 148 | 01/10/2010 | 7:40 | 11:42 | 143.67 | 147.70 | 3.95 | 450,000 | 485 | 218.25 |
| | | 152 | 01/10/2010 | 11:42 | 15:35 | 147.70 | 151.58 | 7.83 | 34,200 | 545 | 18.64 |
| | | 168 | 01/10/2010 | 15:35 | 7:40 | 151.58 | 167.67 | 23.92 | 17,700 | 640 | 11.33 |

(. = no sample analyzed and/or reported)
*End Time for the 8-24 hour collection may occur on the next calendar day
§Time since the first dose on Day 1
Patient #603 did not produce any urine between 4 and 8 hours.

Appendix V
Individual Patient Urinary Excretion Data

| Cohort | Patient | Time Since First Dose (h) | Sample Collection — Start Date | Start Time | End Time* | Sample Data — Start Time§ | End Time§ | Duration (h) | Conc (ng/mL) | Volume (mL) | Amount (mg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | 503 | 148 | 03/16/2010 | 9:28 | 13:43 | 143.22 | 147.47 | 4.13 | 906,000 | 420 | 380.52 |
| | | 152 | 03/16/2010 | 13:43 | 17:25 | 147.47 | 151.17 | 7.83 | 157,000 | 285 | 44.75 |
| | | 168 | 03/16/2010 | 17:25 | 10:00 | 151.17 | 167.75 | 24.42 | 17,200 | 1,290 | 22.19 |
| | 701 | 148 | 03/23/2010 | 8:24 | 12:25 | 142.40 | 146.42 | 3.92 | 503,000 | 320 | 160.96 |
| | | 152 | 03/23/2010 | 12:25 | 16:23 | 146.42 | 150.38 | 7.88 | 198,000 | 350 | 69.30 |
| | | 168 | 03/23/2010 | 16:23 | 8:25 | 150.38 | 166.42 | 23.92 | 46,900 | 600 | 28.14 |
| | 702 | 148 | 03/30/2010 | 9:03 | 13:05 | 142.55 | 146.58 | 3.83 | 443,000 | 830 | 367.69 |
| | | 152 | 03/30/2010 | 13:05 | 17:02 | 146.58 | 150.53 | 7.78 | 59,700 | 300 | 17.91 |
| | | 168 | 03/30/2010 | 17:02 | 9:04 | 150.53 | 166.57 | 23.82 | 31,600 | 510 | 16.12 |
| | 801 | 148 | 03/23/2010 | 8:30 | 11:59 | 144.07 | 147.55 | 3.47 | 1220000 | 350 | 427.00 |
| | | 152 | 03/23/2010 | 11:59 | 16:08 | 147.55 | 151.70 | 7.62 | 239,000 | 210 | 50.19 |
| | | 168 | 03/23/2010 | 16:08 | 8:12 | 151.70 | 167.77 | 23.68 | 22,100 | 985 | 21.77 |

(. = no sample analyzed and/or reported)
*End Time for the 8-24 hour collection may occur on the next calendar day
§Time since the first dose on Day 1
Patient #603 did not produce any urine between 4 and 8 hours.

Appendix V
Individual Patient Urinary Excretion Data

| Cohort | Patient | Time Since First Dose (h) | Sample Collection — Start Date | Start Time | End Time* | Sample Data — Start Time§ | End Time§ | Duration (h) | Conc (ng/mL) | Volume (mL) | Amount (mg) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | 504 | 148 | 04/20/2010 | 9:25 | 13:40 | 143.83 | 148.08 | 4.08 | 549,000 | 525 | 288.23 |
| | | 152 | 04/20/2010 | 13:40 | 17:30 | 148.08 | 151.92 | 7.92 | 166,000 | 395 | 65.57 |
| | | 168 | 04/20/2010 | 17:30 | 9:50 | 151.92 | 168.25 | 24.25 | 46,700 | 530 | 24.75 |
| | 703 | 148 | 04/27/2010 | 9:08 | 13:08 | 143.43 | 147.43 | 3.88 | 605,000 | 800 | 484.00 |
| | | 152 | 04/27/2010 | 13:08 | 17:08 | 147.43 | 151.43 | 7.88 | 88,300 | 590 | 52.10 |
| | | 168 | 04/27/2010 | 17:08 | 9:08 | 151.43 | 167.43 | 23.88 | 27,000 | 1,500 | 40.50 |
| | 704 | 148 | 04/28/2010 | 8:26 | 12:26 | 142.73 | 146.73 | 3.93 | 1470000 | 450 | 661.50 |
| | | 152 | 04/28/2010 | 12:26 | 16:26 | 146.73 | 150.73 | 7.93 | 447,000 | 330 | 147.51 |
| | | 168 | 04/28/2010 | 16:26 | 8:22 | 150.73 | 166.67 | 23.87 | 90,800 | 390 | 35.41 |
| | 802 | 148 | 04/20/2010 | 8:30 | 12:30 | 145.08 | 149.08 | 3.98 | 1550000 | 430 | 666.50 |
| | | 152 | 04/20/2010 | 12:30 | 16:30 | 149.08 | 153.08 | 7.98 | 276,000 | 275 | 75.90 |
| | | 168 | 04/20/2010 | 16:30 | 8:30 | 153.08 | 169.08 | 23.98 | 18,600 | 1,210 | 22.51 |

(. = no sample analyzed and/or reported)
*End Time for the 8-24 hour collection may occur on the next calendar day
§Time since the first dose on Day 1
Patient #603 did not produce any urine between 4 and 8 hours.

Appendix VI
Individual Patient Pharmacokinetic Parameters

| Cohort | Patient | CMAX (ng/mL) | TMAX (h) | AUC(0-24) (hxng/mL) | Regression Start Time Nominal | Regression Start Time Actual | Final Time C>=LOQ | No. Points in Regr | Regr $r^2$ | Lambda_z (/h) | $t_{½}$ (h) | CL/F (mL/min) | Vz/F (L) | Ue(0-24) (mg) | Ue(0-24) (% Dose) | CLr (mL/min) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 101 | 9,250.00 | 1.50 | 35,341.27 | 23.50 | 23.80 | 72.05 | 3 | 0.9928 | 0.02926 | 23.69 | 70.74 | 145.06 | 38.2 | 25.5 | 18.02 |
| | 501 | 4,010.00 | 0.73 | 9,170.88 | 3.50 | 4.00 | 24.40 | 3 | 0.9381 | 0.15609 | 4.44 | 272.60 | 104.79 | 72.5 | 48.3 | 131.68 |
| | 601 | 5,040.00 | 1.50 | 14,296.74 | 24.00 | 24.00 | 72.00 | 3 | 0.9981 | 0.03500 | 19.81 | 174.86 | 299.80 | 58.3 | 38.9 | 68.00 |
| | 603 | 5,340.00 | 1.50 | 19,095.54 | 24.00 | 24.00 | 72.00 | 3 | 0.9959 | 0.04151 | 16.70 | 130.92 | 189.23 | 95.2 | 63.5 | 83.11 |
| 2 | 102 | 15,600.00 | 1.50 | 41,651.97 | 24.00 | 26.08 | 74.00 | 3 | 0.9817 | 0.03078 | 22.52 | 160.06 | 311.96 | 263.3 | 65.8 | 105.36 |
| | 502 | 12,400.00 | 0.73 | 24,873.09 | 8.00 | 8.00 | 48.28 | 3 | 0.9885 | 0.07700 | 9.00 | 335.03 | 261.06 | 176.1 | 35.2 | 117.99 |
| | 604 | 21,000.00 | 1.00 | 89,378.38 | 24.00 | 24.08 | 192.07 | 4 | 0.9963 | 0.01941 | 35.70 | 55.94 | 172.90 | 116.3 | 38.8 | 21.69 |
| | 605 | 11,000.00 | 1.50 | 23,759.10 | 24.00 | 24.00 | 72.00 | 3 | 0.9606 | 0.04227 | 16.40 | 350.74 | 497.82 | 248.2 | 49.6 | 174.12 |
| 3 | 503 | 42,500.00 | 0.50 | 66,705.62 | 24.00 | 24.55 | 72.25 | 3 | 0.9423 | 0.02633 | 26.32 | 249.85 | 569.28 | 447.5 | 44.7 | 111.80 |
| | 701 | 33,000.00 | 1.50 | 145,367.44 | 24.00 | 24.28 | 192.83 | 4 | 0.9965 | 0.01958 | 35.40 | 91.72 | 281.09 | 258.4 | 32.3 | 29.63 |
| | 702 | 38,100.00 | 0.50 | 69,627.87 | 23.90 | 23.98 | 71.98 | 3 | 1.0000 | 0.04841 | 14.32 | 263.30 | 326.32 | 401.7 | 36.5 | 96.16 |
| | 801 | 39,300.00 | 1.52 | 87,341.13 | 7.90 | 7.97 | 47.63 | 3 | 0.9903 | 0.07413 | 9.35 | 219.45 | 177.61 | 499.0 | 43.4 | 95.21 |
| 4 | 504 | 77,300.00 | 1.50 | 170,181.95 | . | . | 192.42 | . | . | . | . | 161.59 | . | 378.5 | 22.9 | 37.07 |
| | 703 | 77,400.00 | 0.77 | 154,072.80 | 23.90 | 23.92 | 71.58 | 3 | 0.9633 | 0.04451 | 15.57 | 156.85 | 211.43 | 576.6 | 39.8 | 62.37 |
| | 704 | 90,300.00 | 1.52 | 205,275.92 | 23.90 | 23.97 | 71.83 | 3 | 0.9843 | 0.03163 | 21.91 | 113.67 | 215.59 | 844.4 | 60.3 | 68.56 |
| | 802 | 28,000.00 | 2.17 | 100,777.13 | . | . | 245.70 | . | . | . | . | 256.34 | . | 764.9 | 49.3 | 126.50 |

(. = parameter could not be estimated)

Appendix VII
Descriptive Statistics for Pharmacokinetic Parameters

| Cohort | Parameter | Units | N | N Missing | Mean | Standard Deviation | Minimum | Median | Maximum | CV (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | CMAX | ng/mL | 4 | 0 | 5,910.0000 | 2,298.3617 | 4,010.0000 | 5,190.0000 | 9,250.0000 | 38.89 |
| | TMAX | h | 4 | 0 | 1.3083 | 0.3833 | 0.7333 | 1.5000 | 1.5000 | 29.30 |
| | AUC(0-24) | hxng/mL | 4 | 0 | 19,476.1083 | 11,326.5426 | 9,170.8817 | 16,696.1408 | 35,341.2700 | 58.16 |
| | LAMBDA_Z | 1/h | 4 | 0 | 0.0655 | 0.0606 | 0.0293 | 0.0383 | 0.1561 | 92.61 |
| | THALF | h | 4 | 0 | 16.1588 | 8.3194 | 4.4407 | 18.2520 | 23.6907 | 51.49 |
| | CL/F | mL/min | 4 | 0 | 162.2816 | 85.0343 | 70.7388 | 152.8928 | 272.6019 | 52.40 |
| | Vz/F | L | 4 | 0 | 184.7203 | 84.1139 | 104.7873 | 167.1472 | 299.7996 | 45.54 |
| | UE(0-24) | mg | 4 | 0 | 66.0517 | 23.9923 | 38.2030 | 65.3934 | 95.2168 | 36.32 |
| | FE(0-24) | %Dose | 4 | 0 | 44.0344 | 15.9949 | 25.4687 | 43.5956 | 63.4779 | 36.32 |
| | CLr | mL/min | 4 | 0 | 75.2005 | 46.8148 | 18.0162 | 75.5506 | 131.6845 | 62.25 |
| 2 | CMAX | ng/mL | 4 | 0 | 15,000.0000 | 4,439.2192 | 11,000.0000 | 14,000.0000 | 21,000.0000 | 29.59 |
| | TMAX | h | 4 | 0 | 1.1833 | 0.3815 | 0.7333 | 1.2500 | 1.5000 | 32.24 |
| | AUC(0-24) | hxng/mL | 4 | 0 | 44,915.6350 | 30,751.0929 | 23,759.1000 | 33,262.5325 | 89,378.3750 | 68.46 |
| | LAMBDA_Z | 1/h | 4 | 0 | 0.0424 | 0.0249 | 0.0194 | 0.0365 | 0.0770 | 58.78 |
| | THALF | h | 4 | 0 | 20.9049 | 11.3086 | 9.0016 | 19.4565 | 35.7050 | 54.10 |
| | CL/F | mL/min | 4 | 0 | 225.4438 | 142.2630 | 55.9419 | 247.5452 | 350.7428 | 63.10 |
| | Vz/F | L | 4 | 0 | 310.9332 | 137.1980 | 172.8988 | 286.5059 | 497.8222 | 44.12 |
| | UE(0-24) | mg | 4 | 0 | 200.9790 | 68.0779 | 116.3090 | 212.1535 | 263.3000 | 33.87 |
| | FE(0-24) | %Dose | 4 | 0 | 47.3640 | 13.7525 | 35.2180 | 44.2065 | 65.8250 | 29.04 |
| | CLr | mL/min | 4 | 0 | 104.7897 | 62.9476 | 21.6885 | 111.6747 | 174.1207 | 60.07 |
| 3 | CMAX | ng/mL | 4 | 0 | 38,225.0000 | 3,947.4675 | 33,000.0000 | 38,700.0000 | 42,500.0000 | 10.33 |
| | TMAX | h | 4 | 0 | 1.0042 | 0.5822 | 0.5000 | 1.0000 | 1.5167 | 57.98 |
| | AUC(0-24) | hxng/mL | 4 | 0 | 92,260.5146 | 36,559.7027 | 66,705.6167 | 78,484.5000 | 145,367.4417 | 39.63 |
| | LAMBDA_Z | 1/h | 4 | 0 | 0.0421 | 0.0246 | 0.0196 | 0.0374 | 0.0741 | 58.51 |
| | THALF | h | 4 | 0 | 21.3481 | 11.7711 | 9.3500 | 20.3194 | 35.4035 | 55.14 |
| | CL/F | mL/min | 4 | 0 | 206.0816 | 78.4162 | 91.7216 | 234.6500 | 263.3045 | 38.05 |
| | Vz/F | L | 4 | 0 | 338.5739 | 165.9217 | 177.6096 | 303.7026 | 569.2808 | 49.01 |
| | UE(0-24) | mg | 4 | 0 | 401.6319 | 103.4205 | 258.4000 | 424.5845 | 498.9585 | 25.75 |
| | FE(0-24) | %Dose | 4 | 0 | 39.2382 | 5.8616 | 32.3000 | 39.9537 | 44.7453 | 14.94 |
| | CLr | mL/min | 4 | 0 | 83.1986 | 36.5158 | 29.6261 | 95.6852 | 111.7979 | 43.89 |
| 4 | CMAX | ng/mL | 4 | 0 | 68,250.0000 | 27,519.0237 | 28,000.0000 | 77,350.0000 | 90,300.0000 | 40.32 |
| | TMAX | h | 4 | 0 | 1.4875 | 0.5721 | 0.7667 | 1.5083 | 2.1667 | 38.46 |
| | AUC(0-24) | hxng/mL | 4 | 0 | 157,576.9500 | 43,484.0035 | 100,777.1333 | 162,127.3750 | 205,275.9167 | 27.60 |
| | LAMBDA_Z | 1/h | 2 | 2 | 0.0381 | 0.0091 | 0.0316 | 0.0381 | 0.0445 | 23.92 |
| | THALF | h | 2 | 2 | 18.7420 | 4.4825 | 15.5724 | 18.7420 | 21.9116 | 23.92 |
| | CL/F | mL/min | 4 | 0 | 172.1133 | 60.1492 | 113.6681 | 159.2220 | 256.3412 | 34.95 |
| | Vz/F | L | 2 | 2 | 213.5136 | 2.9436 | 211.4321 | 213.5136 | 215.5950 | 1.38 |
| | UE(0-24) | mg | 4 | 0 | 641.1178 | 207.9768 | 378.5460 | 670.7515 | 844.4220 | 32.44 |
| | FE(0-24) | %Dose | 4 | 0 | 43.0930 | 15.8418 | 22.9422 | 44.5570 | 60.3159 | 36.76 |
| | CLr | mL/min | 4 | 0 | 73.6267 | 37.7899 | 37.0727 | 65.4664 | 126.5012 | 51.33 |

Arithmetic mean and standard deviation.

Appendix VIII
Fit of the Power Model to Cmax and AUC(0-24) vs. Total Dose

The NLIN Procedure
Dependent Variable CMAX
Method: Gauss-Newton

Iterative Phase

| Iter | a | b | Sum of Squares |
|---|---|---|---|
| 0 | 1.0000 | 1.0000 | 2.674E10 |
| 1 | 1.5988 | 1.2733 | 1.629E10 |
| 2 | 3.6040 | 1.1649 | 1.593E10 |
| 3 | 10.8875 | 1.0703 | 1.114E10 |
| 4 | 17.0039 | 1.1560 | 4.5272E9 |
| 5 | 17.7825 | 1.1228 | 3.0914E9 |
| 6 | 18.4515 | 1.1144 | 3.078E9 |
| 7 | 18.5123 | 1.1140 | 3.078E9 |
| 8 | 18.5139 | 1.1140 | 3.078E9 |

NOTE: Convergence criterion met.

Estimation Summary

| | |
|---|---|
| Method | Gauss-Newton |
| Iterations | 8 |
| Subiterations | 5 |
| Average Subiterations | 0.625 |
| R | 2.88E-7 |
| PPC(a) | 2.262E-6 |
| RPC(a) | 0.000086 |
| Object | 3.47E-10 |
| Objective | 3.078E9 |
| Observations Read | 16 |
| Observations Used | 16 |
| Observations Missing | 0 |

NOTE: An intercept was not specified for this model.

| Source | DF | Sum of Squares | Mean Square | F Value | Approx Pr > F |
|---|---|---|---|---|---|
| Model | 2 | 2.483E10 | 1.242E10 | 56.47 | <.0001 |
| Error | 14 | 3.078E9 | 2.1986E8 | | |
| Uncorrected Total | 16 | 2.791E10 | | | |

All cohorts were combined for this analysis

Appendix VIII
Fit of the Power Model to Cmax and AUC(0-24) vs. Total Dose

The NLIN Procedure

| Parameter | Estimate | Approx Std Error | Approximate 95% Confidence Limits | |
|---|---|---|---|---|
| a | 18.5139 | 38.8544 | -64.8203 | 101.8 |
| b | 1.1140 | 0.2927 | 0.4861 | 1.7418 |

Approximate Correlation Matrix

| | a | b |
|---|---|---|
| a | 1.0000000 | -0.9989944 |
| b | -0.9989944 | 1.0000000 |

All cohorts were combined for this analysis

Appendix VIII
Fit of the Power Model to Cmax and AUC(0-24) vs. Total Dose

The NLIN Procedure
Dependent Variable AUC24
Method: Gauss-Newton

Iterative Phase

| Iter | a | b | Sum of Squares |
|---|---|---|---|
| 0 | 1.0000 | 1.0000 | 1.531E11 |
| 1 | 3.6876 | 0.8351 | 1.527E11 |
| 2 | 19.2061 | 1.1218 | 5.876E10 |
| 3 | 30.6632 | 1.0585 | 5.759E10 |
| 4 | 54.2280 | 0.9837 | 5.5E10 |
| 5 | 129.0 | 0.8746 | 4.88E10 |
| 6 | 210.5 | 0.8921 | 2.01E10 |
| 7 | 218.5 | 0.8870 | 2.01E10 |
| 8 | 219.5 | 0.8865 | 2.01E10 |
| 9 | 219.5 | 0.8864 | 2.01E10 |

NOTE: Convergence criterion met.

Estimation Summary

| | |
|---|---|
| Method | Gauss-Newton |
| Iterations | 9 |
| Subiterations | 9 |
| Average Subiterations | 1 |
| R | 4.817E-6 |
| PPC(a) | 0.000033 |
| RPC(a) | 0.000359 |
| Object | 3.615E-9 |
| Objective | 2.01E10 |
| Observations Read | 16 |
| Observations Used | 16 |
| Observations Missing | 0 |

NOTE: An intercept was not specified for this model.

All cohorts were combined for this analysis

Appendix VIII
Fit of the Power Model to Cmax and AUC(0-24) vs. Total Dose

The NLIN Procedure

| Source | DF | Sum of Squares | Mean Square | F Value | Approx Pr > F |
|---|---|---|---|---|---|
| Model | 2 | 1.358E11 | 6.788E10 | 47.28 | <.0001 |
| Error | 14 | 2.01E10 | 1.4357E9 | | |
| Uncorrected Total | 16 | 1.559E11 | | | |

| Parameter | Estimate | Approx Std Error | Approximate 95% Confidence Limits | |
|---|---|---|---|---|
| a | 219.5 | 401.4 | -641.4 | 1080.5 |
| b | 0.8864 | 0.2570 | 0.3352 | 1.4376 |

Approximate Correlation Matrix

| | a | b |
|---|---|---|
| a | 1.0000000 | -0.9984171 |
| b | -0.9984171 | 1.0000000 |