Plasma Pharmacokinetic (PK) Profile of Two Consecutive Doses of Ferumoxytol in Healthy Subjects

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Background

Ferumoxytol is a carbohydrate-coated superparamagnetic iron oxide nanoparticle being evaluated for safety and efficacy in two distinct areas of medical need:

- As an iron replacement therapy in anemic patients with chronic kidney disease (CKD), both on dialysis and not on dialysis
- As a vascular contrast agent for use with magnetic resonance imaging (MRI).

Iron deficiency anemia is common in chronic kidney disease (CKD); it develops early in the course of disease and affects almost every patient with stage 5 CKD[1]. Intravenous (IV) iron is often required, but available formulations are inconvenient, since they are administered in multiple small doses and via infusions to limit potentially severe adverse events.[2,3]

In patients with CKD, iodinated contrast agents and gadolinium carry the risk of contrast nephropathy and nephrogenic systemic fibrosis, respectively.[4,5] The lack of safe and effective imaging agents for the CKD population severely impacts the ability to accurately diagnose vascular disease in these patients, which in turn limits therapeutic options.

Ferumoxytol was designed to minimize potential immunologic reactions.[6] Ferumoxytol is a stable iron-carbohydrate complex and preliminary data suggest that ferumoxytol is associated with less free iron than other commercially available IV iron-carbohydrate compounds.[7] These properties allow ferumoxytol to be administered as a rapid IV push at a rate of 30 mg/sec.

Preliminary PK data demonstrate that ferumoxytol exhibits dose-dependent, capacity-limited elimination, probably via uptake into the reticuloendothelial system.[6] Previous studies of the pharmacokinetics of other commonly used intravenous compounds have examined changes in the iron pool using conventional measures of iron status, including serum iron and transferrin bound iron after IV iron administration.[7] Some studies have used ratios derived from *ex vivo* treatment of serum samples to determine serum iron versus iron from the iron-carbohydrate complex.[9] These methods make the pharmacokinetic profile of the drug difficult to interpret as they do not directly measure the plasma concentration and disposition of the iron-carbohyrate complex itself.

Ferumoxytol plasma concentrations are determined by a validated, drug-specific nuclear magnetic resonance (NMR) assay. Due to the magnetic properties of ferumoxytol, this bioanalytical method allows for measurement of the intact drug before dissolution and incorporation into iron stores. Thus, exact determination of the PK profile of ferumoxytol can be determined without complicated models derived from iron assays and *ex vivo* treatment of the plasma samples.

The results of a randomized, double blind, placebo-controlled, parallel design, single-center trial of the plasma pharmacokinetics of two consecutive doses of ferumoxytol in healthy

References

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Methods

This was a randomized, double blind, placebo-controlled, parallel design, single-center trial to evaluate the pharmacokinetic and pharmacodynamic profile of ferumoxytol in healthy subjects. (ClinicalTrials.gov identifier NCT00255437).

Subjects were randomized to receive either moxifloxacin, ferumoxytol or placebo. A total of 58 subjects received two 510 mg doses ferumoxytol administered in the supine position as an IV push over 17 seconds 24 hours apart, and formed the cohort for the PK analysis. Eligibility criteria are presented in Table 1.

Subject characteristics at baseline were (mean ± SD): age 30± 8 years, weight 77±12.7 kg and BMI 26± 2.8 kg/m^2. The study population included 24 females and 34 males. Most patients were African American (79.3%), 13.8% were Caucasian, 5.2% Hispanic, and 1.7% Asian.

Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria:
– Male and female, ages 18 to 45 years
– Women of childbearing potential were non-pregnant, non-lactating; negative pregnancy test; appropriate birth control.
– Provided informed consent and signed HIPAA
– Hemoglobin ≥10.0 g/d and ≤16 g/dL for males, ≥10.0 g/d and ≤14 g/dL for females
– Transferrin saturation ≤35%; serum ferritin ≤100 ng/dL
– No clinically significant abnormality on physical exam, ECG, medical history or clinical laboratory testing.

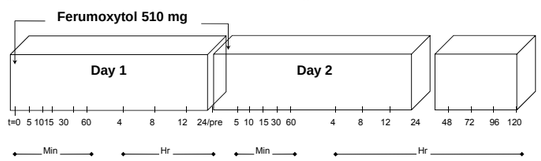
Exclusion Criteria:
– Received another investigational drug or device within 30 days or 5 half-lives (whichever was longer) prior to study.
– Parenteral or oral iron therapy within 30 days prior to dosing
– Acute GI bleeding
– Active infection; positive HIV, Hepatitis B surface antigen or Hepatitis C antibody
– Abnormal liver function tests
– Malignancy (except for non-melanoma of the skin) unless curative treatment and disease free for > 2 years
– Risk factors for Torsades des pointes
– Angina
– Unable to stop smoking during the study
– Excessive consumption of products with xanthine or caffeine
– Regular alcohol consumption
– Any allergies to iron products
– Medication use (other than tylenol, contraceptive, MVI without Fe) within 7 days or 5 half-lives prior to randomization
– Medical condition precluding study participation
– Clinically significant lab abnormality on screening
– Any conditions affecting drug absorption
– Donation of blood or blood components within 4 weeks of study
– Illegal drug use or abuse within the last 2 years

Drug Administration and Plasma Sampling for PK Analysis
Plasma samples for ferumoxytol concentrations were obtained on Day 1 and Day 2 pre-dose and post-dose at 5, 10, 15, 30 minutes and at 1, 4, 8, 12, 24, 48, 72, 96 and 120 hours.

Plasma ferumoxytol concentrations were determined using magnetic resonance relaxivity measurements. Figure 1 details the drug administration schedule and sampling time points.

Statistical Methods
Population PK analyses using zero-order input and Michaelis-Menten elimination were explored in both one and two compartment open models using NONMEM® Version 6, Level 1.0 with NM-TRAN, Version III, Level 1.1 and PREDPP, Version IV, Level 1.1. Model parameters were estimated using the first-order conditional estimation (FOCE) method with interaction. In addition, a noncompartmental analysis of a simulated 2 x 510 mg ferumoxytol dose profile was performed to calculate a time-averaged clearance and the terminal $t_{1/2}$ Data were analyzed using SAS® Version 8.2, and S-PLUS® Server Version 7.

Fig 1. Ferumoxytol Administration and Sampling Timepoints for PK Analysis

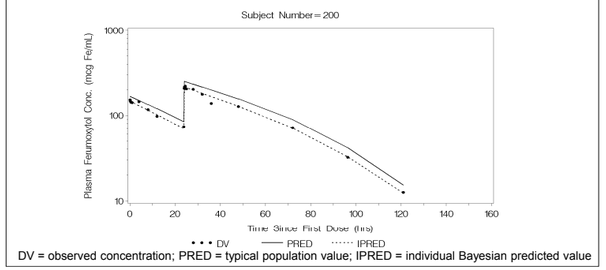


Results

Initial observation of the plasma ferumoxytol concentrations versus time curves plotted with a logarithmic y-axis showed a curved behavior that is characteristic of a capacity-limited elimination process.

A two-compartment open model with non-linear elimination from the central compartment was used to determine V_1, V_{max}, K_m, V_2 and Q (For definitions see Parameters Table 3). The model was further adjusted for the effect of weight on the volume of distribution of the central compartment (V_2), which reduced intersubject variability in V_1 by 26.3%. Figure 2, 3 and 4 demonstrate the model fit.

Figure 2: Sample Overlay Plot of Individual Subject's Data on Model Predicted Values – Plasma Ferumoxytol Log Concentration versus Time



DV = observed concentration; PRED = typical population value; IPRED = individual Bayesian predicted value

Figure 3. Plasma Ferumoxytol Log-Concentration versus Time

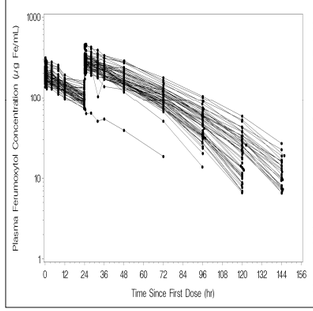
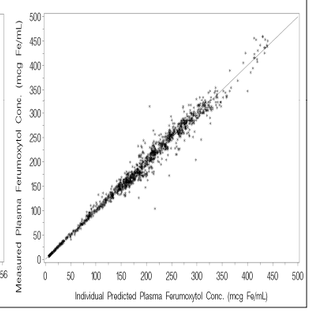


Figure 4. Measured vs. Model Predicted Ferumoxytol Plasma Concentrations



Tables 2 and 3 provide the determined plasma PK parameters and population PK parameter estimates. In addition, a noncompartmental analysis of a simulated 2 x 510 mg ferumoxytol dose profile was performed to calculate a time-averaged clearance and the terminal $t_{1/2}$ was calculated from the terminal slope on Day 2 (Table 4).

The typical value prediction of Day 2 C_{max} is 281 μg/mL. The maximum elimination rate (V_{max}) is 14.3 mg/hr and the Km is 77.49 mg/L.

Table 2: Plasma Pharmacokinetic Parameters for Day 1 and Day 2 Doses of Ferumoxytol

Pharmacokinetic Parameter	Day 1	Day 2
C_{max} (mcg/mL)	206 ± 41.3	301 ± 52.2
t_{max} (hours)	0.32 ± 0.72	0.6 ± 1.24

Data are reported as mean ± SD. Cmax = maximum plasma concentration, tmax = time to maximum plasma concentration

Table 3: Pharmacokinetic Parameter Estimates* - Two-Compartment, Zero-Order Model

	Population Mean		Magnitude of Interindividual Variability (%CV)	
Parameter	**Final Estimate**	**% SEM**	**Final Estimate**	**%SEM**
Central Volume of Distribution (V_1) (L)	2.71	1.8	12	16.6
Maximum Elimination Rate (V_{max}) (mg/hr)	14.3	1.3	10	35.8
Michaelis-Menten Constant (Km) (mg)	210	7.5	14.7	59.3
Distribution Clearance (Q) (L/hr)	0.0221	16.6	72.39	46.4
Peripheral Volume of Distribution (V_2) (L)	0.443	17.4	41.83	32.2
Slope of Relation Between Weight and V_1 (L/kg)	0.0228	14.8	-----	-----
Residual Variability (%CV)	7.07	15.9	-----	-----

*Weight normalized; Min. value of objective function = 7826.709; SEM, standard error of mean; Km = 77.49 mg/L

Table 4: PK Parameter Estimates from a Simulated 2 x 510 mg Ferumoxytol Dose Profile*

Parameter (Units)	Noncompartmental Analysis Result
Terminal $t_{1/2}$ (hour)	15.8
$AUC_{0\text{-}24}$ (mcg·hr/mL)	3260
$AUC_{0\text{-}\infty}$ (mcg·hr/mL)	14,800
Cl (mL/hr)	69.1

*The profile for noncompartmental analysis was simulated using the typical parameter estimates from the NONMEM analysis with the two-compartment model and Michaelis-Menten elimination from the central compartment. The terminal half-life was calculated from the slope of the Day 2 concentrations.

$t_{1/2}$ = half-life, AUC = area under the concentration-time curve, Cl = time-averaged clearance

Summary & Conclusions

The pharmacokinetics of ferumoxytol when administered IV as two 510 mg doses separated by a 24-hour interval are best described using a two-compartment, capacity-limited elimination model. The addition of weight as a covariate on central volume of distribution significantly improved the typical value pharmacokinetic parameter predictions

Plasma ferumoxytol half-life is concentration dependent, and decreases as concentrations decrease. In the terminal linear portion of the curve, the typical-value terminal $t_{1/2}$ is 15.8 hr.

The long $t_{1/2}$ and relatively slow clearance of ferumoxytol from the simulated Day 2, 510 mg dose models are consistent with what is expected for the particle size.

The plasma pharmacokinetic profile of ferumoxytol is similar to that of other iron-carbohydrate complexes[9].