

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-180

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

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1 Executive Summary

The applicant submitted an original NDA 22-180 on 12/18/1007 for ferumoxytol, an iron containing compound.

The proposed indication is the treatment of iron deficiency anemia in patients with chronic kidney disease (CKD). The proposed dosage regimen is as follows:

Doses up to 510 mg of ferumoxytol may be given as a rapid intravenous (IV) injection at rates up to 1 ml/sec (30 mg/sec). A second dose up to 510 mg may be administered as soon as 7 days following the first dose.

In support of the proposed indication and dosing regimen, the applicant submitted the data from 11 studies:

- o Three Phase 1 studies evaluating the pharmacokinetics (PK) and safety of ferumoxytol, including a thorough QT study. These studies examined doses ranging from a single 1 mg/kg dose to a regimen of two doses of 510 mg in healthy volunteers and single doses of 125 mg and 250 mg in subjects with CKD.
- o Two Phase 2 studies evaluating the various dose regimens of ferumoxytol (8 x 128 mg; 4 x 255 mg and 2 x 510 mg) for iron replacement in subjects with CKD.
- o Two Phase 2 imaging studies assessing the safety and feasibility of ferumoxytol as a magnetic resonance imaging (MRI) contrast agent.
- o Four Phase 3 randomized, multicenter clinical studies:
 - Three phase 3 active-controlled studies in which the safety and efficacy of ferumoxytol administered a total dose of 1.02 g as 2 x 510 mg or 4 x 255 mg was evaluated.
 - One Phase 3 study was a double-blind, placebo-controlled, cross-over study that evaluated the safety of a single dose of 510 mg ferumoxytol compared to an intravenous (IV) saline control. All these studies enrolled patients of CKD, stages 1-5 and on hemodialysis (5D), including subjects with functioning kidney transplant.

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Among these 11 studies, the clinical pharmacology review is focused on three phase 1 and two phase 2 studies evaluating the various dosing regimen. The two phase 2 studies assessing feasibility of ferumoxytol for MRI imaging were not reviewed because they are not relevant to the proposed indication, and do not include PK information.

1.1 Recommendation

From a clinical pharmacology perspective, the application is acceptable provided that the sponsor and the Agency come to a mutually satisfactory agreement regarding the language in the package insert.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Ferumoxytol consists of a superparamagnetic iron oxide nanoparticle that is surrounded by a carbohydrate shell, which functions to isolate the bioactive iron from plasma components until the iron-carbohydrate complex enters the reticuloendothelial system (RES) macrophages of the liver, spleen and bone marrow. The iron is released from the iron-carbohydrate complex within vesicles in the macrophages. Iron then either enters the intracellular storage iron pool (eg. ferritin) or is transferred to plasma transferrin for transport to erythroid precursor cells for incorporation into hemoglobin.

Ferumoxytol can be administered intravenously at doses up to 510 mg as a rapid injection at rates up to 1 ml/sec. A second dose of ferumoxytol up to 510 mg may be administered as soon as 7 days after the first dose.

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The important findings from a clinical pharmacology perspective are as follows:

- The clearance (CL) of ferumoxytol was reduced with increasing dose. This dose dependent PK of ferumoxytol was best described by two-compartment model with capacity-limited elimination.
- No gender differences were observed. The CL of ferumoxytol in females is 22 % less than that of males. Also volume of distribution (Vd) of ferumoxytol in females is 25 % less than that of males. However, normalization based on weight eliminated these differences. Furthermore, a subgroup analysis of the integrated clinical data showed no significant difference in pharmacodynamic parameters, i.e., increase of hemoglobin from baseline, by gender.
- After cessation of hemodialysis, ferumoxytol concentration in blood reduced substantially indicating that renal contribution on the elimination of ferumoxytol is not significant. The concentration was lower than the same time point in healthy volunteers, suggesting that hemodialysis may remove a small fraction of ferumoxytol. No more PK information of ferumoxytol in hemodialysis patients is necessary because the safety and efficacy of ferumoxytol were evaluated in hemodialysis patients in clinical trials.
- Ferumoxytol did not significantly increase QTc interval after administration of a 2 x 510 mg within 24 hours (i.e., 1.5 times of the proposed dose).
- The rate of injection did not affect the PK of ferumoxytol. This data supports 1 ml/sec injection of 510 mg of ferumoxytol.

- In Phase 2 studies, mean changes from baseline in hemoglobin (Hgb) and transferrin saturation (TSAT) for 8 weeks following the initial dose of study medication were measured. Additionally, the change from baseline was evaluated for hematocrit (Hct), serum iron, serum ferritin, and reticulocytes. The times to maximum response for Hgb, Hct, TSAT, and serum ferritin were secondary efficacy endpoints. To find an appropriate dosing regimen, the parameters of the 2x510 mg dosing regimen were compared to 4 x 255 mg or 8 x 128mg dosing regimens or oral iron supply. All three intravenous dosing regimens appeared to be more effective than oral iron regimen.

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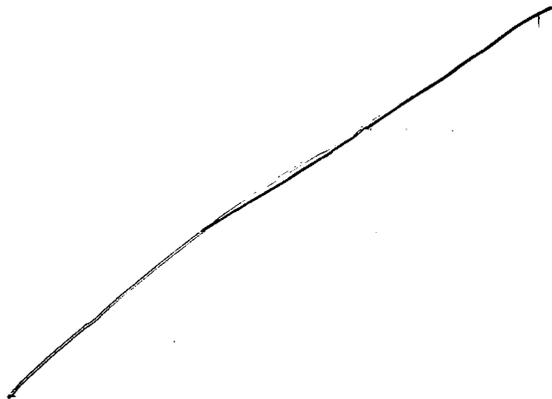
2 Question Based Review

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

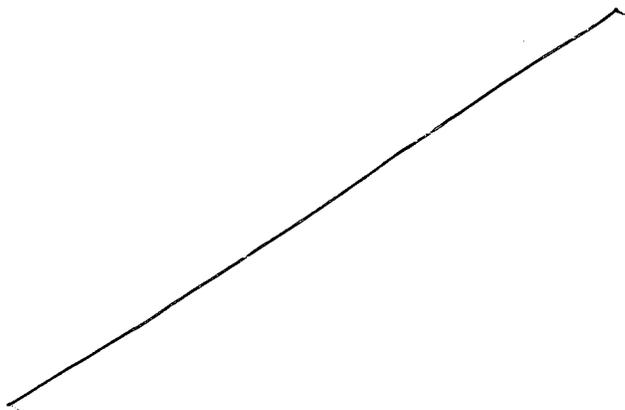
The drug substance in ferumoxytol is a superparamagnetic iron oxide nanoparticle **b(4)** coated with polyglucose sorbitol carboxymethylether formulated with mannitol. The average particle size is less than \rightarrow nanometers.

Figure 1. Crystal structure of iron oxide



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Figure 2. Sketch of polyglucose sorbitol carboxymethylether covered supramagnetic iron oxide



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- Drug Class: Parenteral iron preparation
- Therapeutic Class: Hematinic

- The general formula for the iron oxide: / _____
- The average chemical formula : $Fe_{5874}O_{8752} - C_{11719}H_{18682}O_{9933}Na_{414}$.
- Apparent Molecular Weight: Approximately 750 kDa
- Chemical Name(s):
 - Polyglucose sorbitol carboxymethylether superparamagnetic iron oxide
 - Carboxymethyl poly (glucose)-sorbitol ether superparamagnetic iron oxide

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Ferumoxytol (drug product) is a sterile aqueous colloidal solution that contains 30 mg/mL of elemental iron and 44 mg of mannitol, with low bleomycin-detectable iron. The formulation is isotonic with an osmolality of 270-330 mOsm/kg.

Table 1. Components of ferumoxytol (product)

Component	Concentration per ml	Function
Ferumoxytol drug substance (iron & polyglucose sorbitol carboxymethylether (PSC))	30 mg iron _____	Active source of iron Component of drug substance
Mannitol	44 mg _____	_____
Water for injection	_____	_____

b(4)

The product contains no preservatives and the pH is 6 to 8. The following table shows the dosage form and strength: Ferumoxytol (30 mg/ml) is provided in single use vials in three configurations.

Table 2. The available dosage forms of ferumoxytol (drug product)

Dose (elemental iron) per vial	Volume per vial	Vial size
510 mg	17 mL	_____
255 mg	8.5 mL	_____
127.5 mg	4.25 mL	_____

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Ferumoxytol is isotonic, physiologic pH, low free iron, and minimum immunologic reactivity (the sponsor's opinion). Ferumoxytol is compared to currently available intravenous iron products in the following table.

Table 3. Physicochemical properties of ferumoxytol and comparison to those of other currently available iron intravenous products.

Product	Osmolality (mOsm/kg)	pH	% Free Iron (ultrafiltration)	Average Bleomycin Detectable Iron (mM)	Immunogenicity Potential
Ferumoxytol	297	6 - 8	0.001	1.15 ± 0.46	Low
INFeD® (Iron dextran)	500	5.2 – 6.5	0.298	3.03 ± 0.90	High
Ferlecit® (Sodium ferric gluconate)	990	7.7 – 9.7	2.360	7.26 ± 2.62	Low
Venofer® (Iron sucrose)	1316	10.5 – 11.1	0.038	6.70 ± 1.78	Low

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

MODE OF ACTION

Ferumoxytol consists of a superparamagnetic iron oxide nanoparticle that is surrounded by a carbohydrate shell, which functions to isolate the bioactive iron from plasma components until the iron-carbohydrate complex enters the reticuloendothelial system macrophages of the liver, spleen and bone marrow. Then, the iron is released from the iron-carbohydrate complex within vesicles in the macrophages. Iron then either enters the intracellular storage iron pool (eg. ferritin) or is transferred to plasma transferrin for transport to erythroid precursor cells for incorporation into hemoglobin.

INDICATION

Ferumoxytol should be used for the treatment of iron deficiency anemia in patients with chronic kidney disease (CKD).

2.1.3 What are the proposed dosage(s) and route(s) of administration?

Ferumoxytol can be administered intravenously at doses up to 510 mg as a rapid injection at rates up to 1 mL/sec. A second dose of ferumoxytol up to 510 mg may be administered as soon as 7 days after the first dose.

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2.2 General Clinical Pharmacology

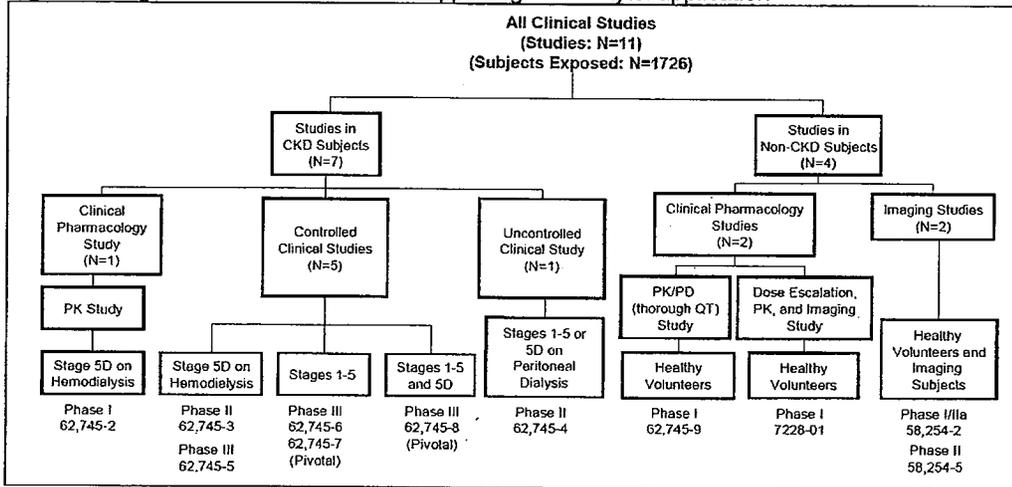
2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Eleven studies support the proposed indication and therapeutic dose of ferumoxytol of 2 x 510 mg in subjects with all stages of CKD (See Figure 3 below for diagram of clinical studies and Appendix 4.4 Tabular listing of clinical studies for detailed design).

A total of 1726 subjects, of whom 1562 had CKD, have been treated with ferumoxytol across the clinical development program with 665 exposed to ferumoxytol in three Phase 3 pivotal efficacy and safety trials; this included subjects not on dialysis (stages 1-5), subjects on hemodialysis (stage 5D), and subjects with functioning kidney transplants.

Efficacy was evaluated in five clinical studies (three pivotal Phase 3 Studies 62,745-5, 62,745-6, and 62,745-7 and two supportive Phase 2 Studies 62,745-3, 62,745-4). Safety was supported by the data from 11 studies conducted in the US under IND 62,745 and IND 58,254. Nine studies were conducted for the use of ferumoxytol as an IV iron replacement therapy; seven of these studies were conducted in subjects across the continuum of CKD stages and provide an accurate and comprehensive safety profile of ferumoxytol in this patient population.

Figure3. Diagram of all clinical studies supporting ferumoxytol application



Study 62,745-2 was designed to investigate the PK of ferumoxytol in hemodialysis patients. Two clinical pharmacology studies were conducted in healthy volunteers: One of which was a Thorough QT Study (62,745-9), and the purpose of the other study was dose escalation-tolerability and to assess the effect of dosing rate on the PK of ferumoxytol (7228-01). Two studies (58,254-2 and 58254-8) were conducted in healthy volunteers or imaging subjects to evaluate the potential use of ferumoxytol as a magnetic resonance angiography (MRA) contrast agent.

The sponsor explored various doses and regimens, including 2 doses of 510 mg each (2 x 510 mg), 4 doses of 255 mg each (4 x 255 mg), or 8 doses of 128 mg each (8 x 128 mg), or a single dose of 125 mg, 250 mg, and 510 mg of ferumoxytol.

The clinical pharmacology review was focused on three phase I studies (62,745-9, 62,745-2, and 7228-01) and 2 phase II studies (62,745-3 and 62,745-4). It should be noted that the interdisciplinary review team (Dr. Joanne Zhang: Biometrics) evaluated the effect of ferumoxytol on QTc from the study 62,745-9.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

Anemia is common in patients with CKD, becoming more prevalent with progressive loss of kidney function. The incidence of anemia is nearly 100% among patients on dialysis. Iron deficiency contributes to anemia in patients with CKD. The etiology of iron deficiency is diverse; possible causes include non-surgical or surgical blood loss, decreased intake

or impaired absorption of dietary iron, iron sequestration due to inflammatory processes, and increased iron utilization in patients on erythropoiesis stimulating agent (ESA) therapy.

The production of erythropoietin, a hormone that promotes red blood cell (RBC) production in the bone marrow, falls in CKD. Anemic patients with CKD are typically treated with ESA therapy, and the available iron stores progressively diminish during erythropoiesis. The increased iron utilization with ESA therapy, in conjunction with blood losses (particularly in the hemodialysis patient), may lead to an absolute iron deficiency. CKD may also be accompanied by inflammation, leading to functional iron deficiency, a state in which the serum markers of body iron stores are relatively normal, but the provision of additional iron results in enhanced erythropoiesis.

Since many CKD patients develop iron deficiency anemia, iron replacement therapy is needed to enable adequate erythropoiesis. Replacement of iron stores with oral iron therapy is limited by relatively poor intestinal absorption and gastrointestinal intolerance. Intravenous iron replacement therapy may instead be used to replenish iron stores. Current guidelines recommend the administration of iron intravenously in hemodialysis patients, and either IV or oral in patient not on dialysis or on peritoneal dialysis. Intravenous iron is typically administered in replacement courses of one gram of iron, and hemodialysis patients typically require a course once every 3 to 6 months in order to maintain recommended serum ferritin and transferrin saturation (TSAT) levels.

Iron deficiency is defined either absolute or functional. Absolute iron deficiency is defined when indicators of iron stores are low, i.e., serum ferritin <100 ng/mL, transferrin saturation [TSAT], also referred to as percent saturation, <20%. Functional iron deficiency does not meet the above laboratory criteria, but demonstrates an increase in hemoglobin (Hgb) or a decrease in ESA dosage with stable Hgb when intravenous (IV) iron is administered.

In Phase 2 studies, the primary efficacy endpoints were the mean changes from baseline in Hgb and TSAT for 8 weeks following the initial dose of study medication. Additionally, the change from baseline was evaluated for hematocrit (Hct), serum iron, serum ferritin, and reticulocytes. The times to maximum response for Hgb, Hct, TSAT, and serum ferritin were secondary efficacy endpoints.

In these studies, the safety of ferumoxytol was assessed on the basis of AEs, clinical laboratory tests (hematology, clinical chemistry, iron panel, and clotting function panel), vital signs (blood pressure, heart rate, respiration rate, and temperature), and physical examinations.

The results of the phase 2 studies showed that the intravenous injection of ferumoxytol up to 2 x 510 mg increased the primary end points and the secondary endpoints appeared preferable to oral iron treatment.

In Phase 3 studies, the primary efficacy endpoint was the mean change from baseline in Hgb at 5 weeks (Day 35 visit) following ferumoxytol administration. Secondary efficacy endpoints included the mean change from baseline in ferritin at 3 weeks (Day 21 visit); Hgb responders; and Hgb and ferritin responders. Other iron-related measures were also evaluated during the study. The results showed that Hgb was increased substantially more following ferumoxytol administration compared to control, i.e., oral iron administration.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The sponsor applied the magnetic resonance imaging technique to measure ferumoxytol in blood as ferumoxytol includes superparamagnetic iron oxide. The magnetic resonance signal intensity of the blood and reticuloendothelial organs over time provides a measure of the presence and clearance of the superparamagnetic iron oxide in ferumoxytol.

Spin-lattice relaxation time (T1) was used to quantify the superparamagnetic iron oxide in ferumoxytol in plasma or serum. The magnetic resonance relaxation rates (1/T1) of plasma appeared proportional to plasma drug concentrations of iron oxide after administration of ferumoxytol. This analytical method were validated by AMAG Pharmaceuticals, Inc. using two different instruments, a Bruker PC-120 nuclear magnetic resonance (NMR) spectrometer with an applied field of 1 Tesla and a Bruker Minispec mq NMR analyzer.

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Using these validated methods, the sponsor determined the PK of ferumoxytol following IV administration to healthy adults in two Phase 1 studies, 7228-01 and 62,745-9, and in a single study involving subjects with CKD, Study 62,745-2.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

The efficacy parameters, e.g., serum iron parameters and TSAT appeared dose dependent (Study 7228-01):

Figure 4. Serum iron concentration after administration of ferumoxytol

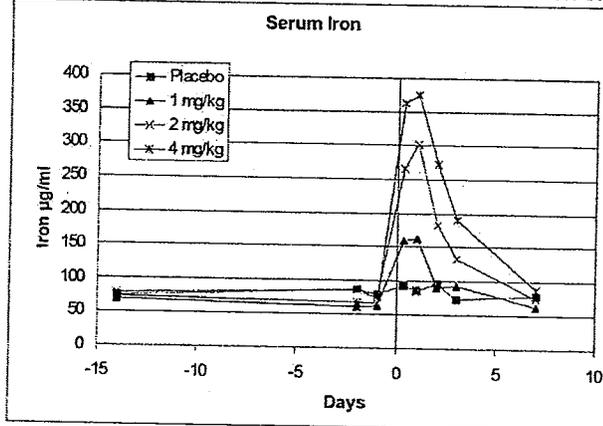


Figure 5. Transferrin saturation after administration of ferumoxytol

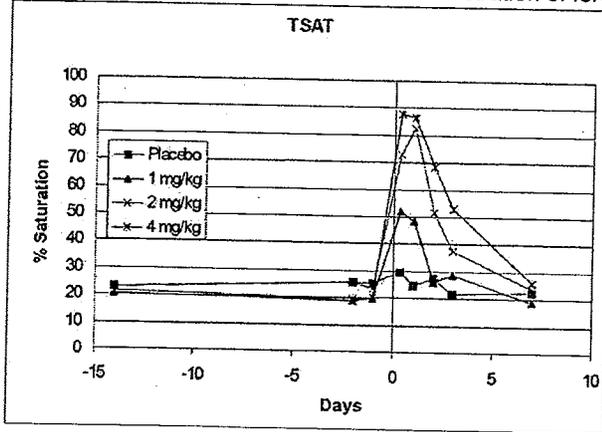
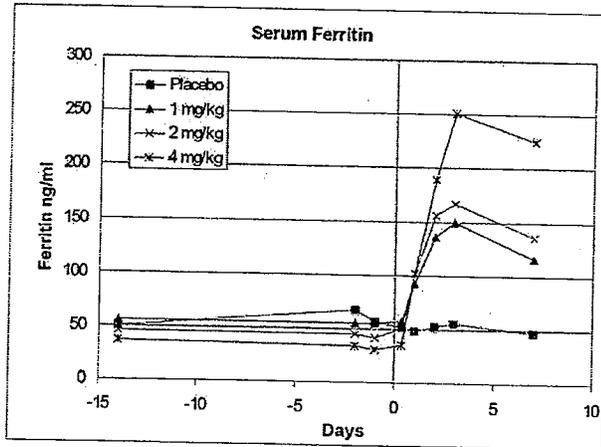


Figure 6. Serum ferritin level after administration of ferumoxytol



A phase 2 study results (627745-3) showed that 2x510 mg dosing regimen appeared to increase hemoglobin and TSA from the baseline more effectively than oral iron regimen:

Figure 7. Mean hemoglobin level following administration of ferumoxytol or oral iron.

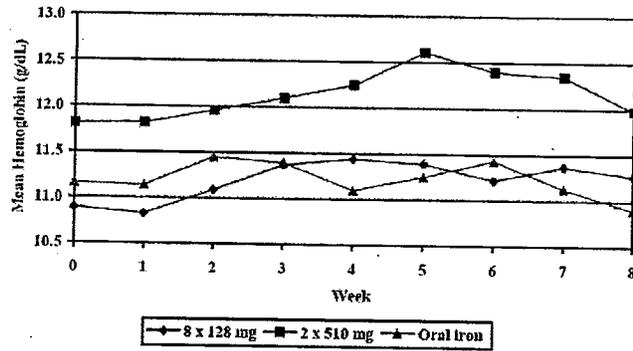
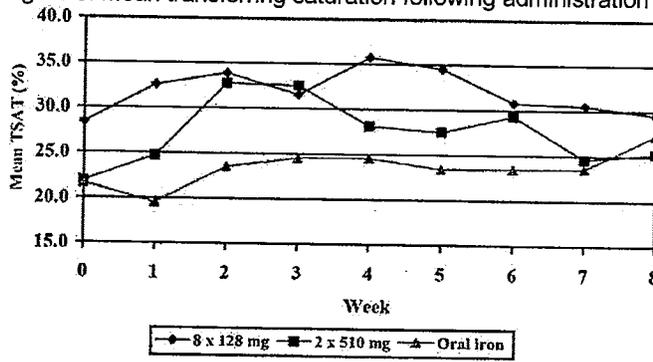


Figure 8. Mean transferrin saturation following administration of ferumoxytol or oral iron



2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

In a phase 2 study (Study 62745-3), the times to maximum response for hemoglobin, hematocrit, TSAT, and serum ferritin were measured as secondary endpoints. The both of intravenous regimen appeared to be preferable to oral iron:

Table 4. Time to Maximum Level of Iron Metabolism Parameters, Hemoglobin, and Hematocrit

Parameter Descriptive Statistics	Ferumoxytol		Oral Iron N = 10
	8 x 128 mg N = 10	2 x 510 mg N = 11	
Time (days) to maximum level of TSAT			
Mean ± SD	26.70 ± 15.30	19.73 ± 15.20	33.50 ± 15.18
Time (days) to maximum level of serum ferritin			
Mean ± SD	23.50 ± 8.09	14.73 ± 8.38	32.20 ± 19.34
Time (days) to maximum level of hemoglobin			
Mean ± SD	34.40 ± 15.52	33.45 ± 12.96	37.10 ± 17.90
Time (days) to maximum level of hematocrit			
Mean ± SD	32.10 ± 17.90	37.09 ± 10.90	36.60 ± 18.19

2.2.4.3 Does the drug prolong the QT or QTc interval?

No significant QT prolongation effect was detected following intravenous (IV) administration of two doses of ferumoxytol 510 mg intravenous within 24 hours. (See the following table). The upper two-sided 90% CI was below 10 ms, the threshold for regulatory concern as described in the ICH E14 guideline. The two 510-mg doses IV within 24 hours (compared to within one week for therapeutic doses) appeared to be a 1.5-fold increase in the mean C_{max} for the therapeutic dose schedule.

The results came from a phase 1 active- and placebo-controlled study of the electrocardiogram effects and pharmacokinetics of ferumoxytol in healthy men and women (62,745-9). A total of 174 subjects (58 subjects in ferumoxytol treatment and Moxifloxacin) were studied. Moxifloxacin (400 mg p.o.) was given as a positive control. A parallel group design was utilized to study a supratherapeutic regimen of two 510 mg doses of ferumoxytol in a blinded fashion compared with two doses of placebo. The sponsor did not explore drug-drug interaction studies. Therefore, there is no information regarding changes in ferumoxytol in the presence of other drugs. Additionally, the study was conducted in healthy volunteers who naturally have higher amounts of iron than patients. The supratherapeutic dose administered in this study appears reasonable to cover the range of iron concentrations observed in the worst case scenario.

There was no relationship between ferumoxytol concentrations and $\Delta\Delta\text{QTcF}$. The overall results are presented in the following table. (Refer to the consult review of Dr. Joane Zhang from IRT QT team in DFS nda 22-180 signed off on 6/27/08)

TABLE 5. THE POINT ESTIMATES AND THE 90% CIs CORRESPONDING TO THE LARGEST UPPER BOUND FOR FERUMOXYTOL AND THE LARGEST LOWER BOUND FOR MOXIFLOXACIN (FDA ANALYSIS*)

Treatment	Time (h)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
Ferumoxytol 2x510 mg	2 hour	-0.51	(-3.37, 2.34)
Moxifloxacin 400 mg	3 hour	12.96	(9.64, 16.29)

* Multiple endpoint adjustment is not applied. The largest lower bound after Bonferroni adjustment was 7.72 ms. There was no relationship between ferumoxytol concentrations and $\Delta\Delta\text{QTcF}$.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The proposed dose and dosing regimen are supported by the result of Phase 1 and 2 studies. There are no unresolved dosing or administration issues.

2.2.5 PK characteristics of the drug and its major metabolite

2.2.5.1 What are the single dose and multiple dose PK parameters?

The pharmacokinetic (PK) behavior of ferumoxytol has been examined in healthy subjects and in patients with CKD stage 5D on hemodialysis.

Ferumoxytol exhibited dose-dependent, capacity-limited elimination from plasma. The sponsor explained that the disappearance of ferumoxytol from plasma is mostly via uptake into the reticuloendothelial system. However, no studies that demonstrate the fate of ferumoxytol were conducted.

The volume of distribution (Vd) was consistent with plasma volume, and the mean maximum observed plasma concentration (C_{max}) and terminal half-life values increased with dose.

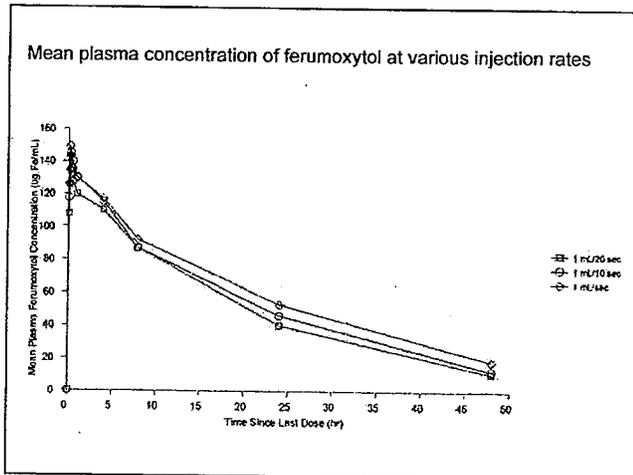
The estimated value for Day 2 plasma terminal half-life following two 510 mg doses of ferumoxytol administered intravenously within 24 hours was 19 hours. Estimated mean clearance values ranged from 69.1 – 265 mL/hr depending upon the dose of ferumoxytol administered, with lower clearance at higher doses.

Table 6. Estimated pharmacokinetic parameters of ferumoxytol after intravenous administration

Study	Study 7228-1			Study 62745-9
Dose	1 mg/kg (85.3 mg)	2 mg/kg (152 mg)	4 mg/kg (316 mg)	Two 510 mg dose
Number of subject	8	8	17	58
AUC _{0-∞} (µg·hr/ml)	365 ± 128	996 ± 313	2930 ± 685	15400 ± 3750
C _{max}	27.0 ± 7.7	62.2 ± 12.0	138 ± 34	206 ± 41
T _{1/2} (hr)	9.7 ± 2.0	11.4 ± 1.6	14.9 ± 2.0	19.0 ± 4.6
CL (ml/hr)	265 ± 118	164 ± 56	110 ± 24	69.1 ± 13.9
Vd (L)	3.45 ± 0.81	2.62 ± 0.67	2.36 ± 0.55	3.16 ± 0.4

The rate of injection had no influence on ferumoxytol PK parameters as shown in the following figure of the plasma concentration profile of ferumoxytol at various injection rate. (Refer to the section 4.2 individual study review on 7728-01)

Figure 9. Mean plasma concentration of ferumoxytol following various injection rates.



2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

PK of ferumoxytol in patients with CKD stage 5D (on hemodialysis) was investigated in study 62745-2. The ferumoxytol concentration during hemodialysis was not reduced during hemodialysis (Refer to Figure 10 below) after administration.

Hemodialysis would not be expected to affect ferumoxytol elimination from plasma because the molecular weight (MW) of ferumoxytol (approximately 750 kDa) is substantially larger than the MW cutoff for hemodialysis apparatus (approximately 65 kDa). It cannot be concluded, however, that ferumoxytol is not dialyzable only based on the minimal or no mean concentration change during hemodialysis because there was substantial fluid loss during hemodialysis (3.3 ± 1.5 kg) which might affect the ferumoxytol concentration.

Due to the lack of blood concentration data between 3 hours and 48 hours after administration of ferumoxytol, PK of ferumoxytol in hemodialysis patients cannot be accurately described.

At 48 hour after administration, ferumoxytol concentration in blood reduced substantially in hemodialysis patients (Refer to the Table 8 below) indicating that renal contribution on the elimination of ferumoxytol is not significant.

No more PK information of ferumoxytol in hemodialysis patients is necessary as the safety and the efficacy of ferrumoxytol were evaluated in hemodialysis patients in clinical trials.

Figure 10. Plasma concentration of ferumoxytol during dialysis

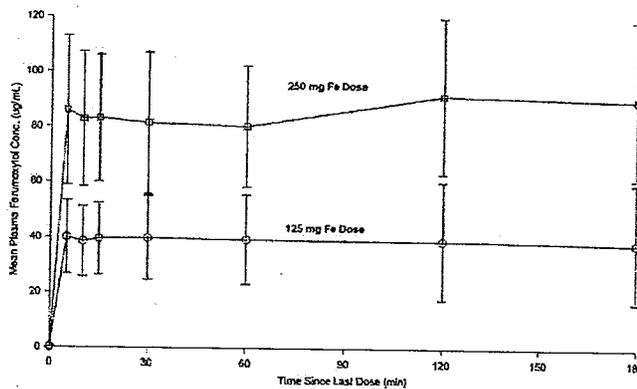


Table 8. Plasma concentration after cessation of hemodialysis

	<p>CKD 5D on hemodialysis</p> <p>(from study 62745-2)</p>
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Dose	125 mg	250 mg
Concentration at 5 min after administration	40.0 ± 13.2 µg/ml (N=10)	85.8 ± 27.1 µg/ml (n=10)
Concentration at 48 hours After administration	BLQ *	6.21 ± 8.4 µg/ml (n=4) **

* BLQ represents below the limit of quantify. In this study, BLQ was 11.6 µg/ml.

** 6 samples were below the BLQ.

2.2.5.3 What are the characteristics of drug absorption?

Not applicable as ferumoxytol is for IV injection.

2.2.5.4 What are the characteristics of drug distribution?

See section 2.2.5.7.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

The mass balance study has not been conducted. (See section 2.2.5.7)

2.2.5.6 What are the characteristics of drug metabolism?

See section 2.2.5.7

2.2.5.7 What are the characteristics of drug excretion?

The sponsor stated that the disappearance of ferumoxytol from plasma is mostly via uptake into the reticuloendothelial system (RES). The observed disappearance of ferumoxytol from blood pool in hemodialysis patients indirectly indicates that the kidneys do not contribute on the excretion of ferumoxytol. However, no studies to determine the fate of ferumoxytol were conducted.

Typically, iron either enters the intracellular storage iron pool (eg. ferritin) or is transferred to plasma transferrin for transport to erythroid precursor cells for incorporation into hemoglobin. Liver or kidneys normally do not eliminate iron. Human body loses only small amount of iron per day (1-2 mg/day) through sloughed mucosal cells and desquamation, and menstruation, etc.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The ferumoxytol PK studies demonstrate that the dose normalized single-dose peak plasma ferumoxytol concentration (C_{max}) and the dose normalized AUC_{0-inf} increased by increasing the dose, indicating non-linear pharmacokinetics.

Figure 11. Dose normalized ferumoxytol Cmax versus dose

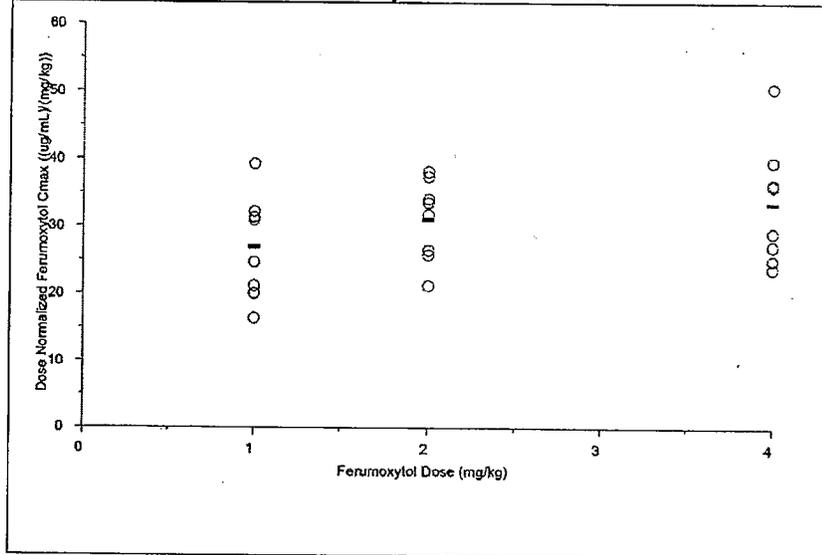
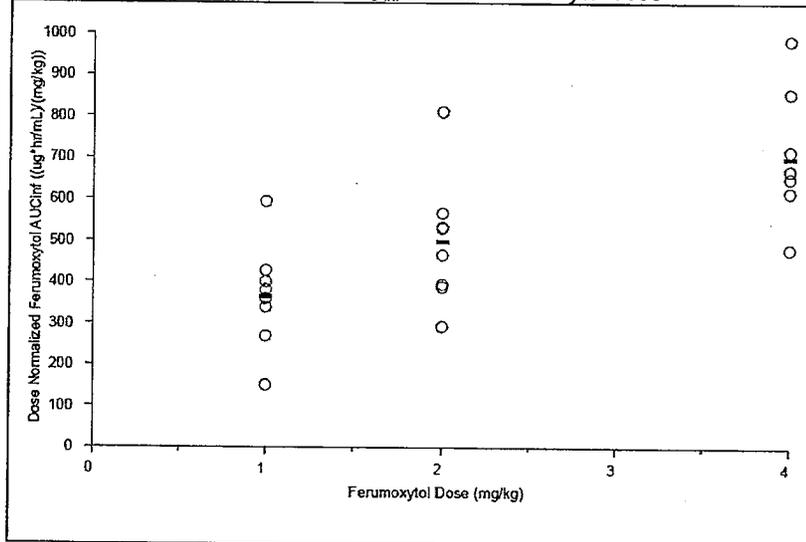


Figure 12. Dose normalized AUC_{0-inf} versus ferumoxytol dose



2.2.5.9 How do the PK parameters change with time following chronic dosing?

As ferumoxytol is to be dosed only twice, an assessment of the PK over time was not necessary.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

No significant differences were seen between males and females when central volume of distribution (V1) and clearance were weight-normalized. The effect of weight on V1 was quantified in the population PK model in Study 62,745-9 following two doses of 510 mg administered within 24 hours (30 mg Fe/mL given at a rate of 1 mL/second over 17 seconds). The addition of weight as a covariate on V1 significantly improved the PK parameter predictions and reduced intersubject variability in V1 by 26.3% (16.28 CV% to 12.00 CV%).

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Other than body weight, no intrinsic or extrinsic factors were identified as important contributors to ferumoxytol PK. (See section 2.2.5.10; 2.3.2.3; and 2.3.2.4)

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

From the clinical pharmacology study, 62,745-9, gender did not affect PK parameters once normalized to weight (See section 2.3.2.3). A subgroup analysis of the integrated data set from phase 3 studies provides the information on the effect of intrinsic factors on drug effect.

In the following table, baseline Hgb and the mean change from baseline in Hgb at Week 5 are presented by treatment group and demographic subgroups (ie, age, gender, race, geographic region) for the integrated analyses across all randomized clinical phase 3 trials. Analysis of the mean change from baseline in Hgb at Week 5 across the demographic subgroups of age, gender, race, geographic region demonstrated that 2 x 510 mg ferumoxytol increased hemoglobin in iron deficiency anemia regardless of subgroup.

Table 9. Mean change of hemoglobinat 5 weeks after administration of ferumoxytol 2 x 510 mg or 4 x 255 mg or oral iron 200 mg/day

	Ferumoxytol 2 x 510 mg			Ferumoxytol 4 x 255 mg			Oral Iron 200 mg/day		
	N	Baseline (g/dL) Mean±SD	Week 5 Change from Baseline (g/dL) Mean±SD	N	Baseline (g/dL) Mean±SD	Week 5 Change from Baseline (g/dL) Mean±SD	N	Baseline (g/dL) Mean±SD	Week 5 Change from Baseline (g/dL) Mean±SD
Age									
<50 years	105	10.22±0.96	1.06±1.38	18	11.02±0.71	0.66±0.80	38	10.16±0.96	0.58±1.42
50 to <65 years	192	10.14±0.80	1.00±1.13	20	11.07±0.60	1.15±1.49	112	10.40±0.79	0.43±1.07
65 to <75 years	163	10.14±0.76	0.94±1.20	12	11.13±0.53	0.49±0.91	70	10.33±0.75	0.46±0.89
≥75 years	145	10.10±0.74	1.17±1.27	10	11.32±0.42	1.28±1.10	59	10.28±0.69	0.25±0.89
Gender									
Male	258	10.15±0.84	1.17±1.27	26	11.09±0.57	0.75±1.02	130	10.37±0.78	0.47±1.11
Female	347	10.15±0.78	0.93±1.18	34	11.12±0.61	1.00±1.25	149	10.28±0.79	0.38±0.99
Race									
Caucasian	332	10.11±0.77	1.11±1.24	21	11.12±0.60	1.03±1.04	138	10.29±0.77	0.28±1.00
Black or African-American	238	10.20±0.83	0.94±1.21	32	11.09±0.55	0.64±1.05	128	10.36±0.80	0.59±1.10
Other	35	10.08±0.92	0.96±1.26	7	11.13±0.82	1.63±1.68	13	10.42±0.81	0.16±0.71
Geographic Region									
Northeast	117	10.40±0.80	1.19±1.20	25	10.97±0.64	0.82±1.07	72	10.29±0.86	0.40±1.00
Midwest	91	10.09±0.66	1.16±1.33	1	10.75	-0.55	52	10.27±0.72	0.43±1.02
South	317	10.03±0.83	0.97±1.22	20	11.13±0.54	0.72±1.09	117	10.30±0.79	0.49±1.10
West	80	10.29±0.77	0.90±1.13	14	11.34±0.55	1.36±1.32	38	10.54±0.69	0.22±0.99

Abbreviations: ITT=intent-to-treat; SD=standard deviation.

Data Source: Statistical Table 16.1.1, Statistical Table 16.1.5, Statistical Table 17.1.1, Statistical Table 17.1.5, Statistical Table 18.1.1, Statistical Table 18.1.5, Statistical Table 19.1.1, and Statistical Table 19.1.5

2.3.2.1 Elderly

No geriatric clinical pharmacology studies were submitted with this application.

2.3.2.2 Pediatric patients

No pediatric clinical pharmacology studies were submitted with this application. For pediatrics of 0 to 2 years old, the study is waived, and for pediatrics of 2 to ~~4~~ years old, the study has been deferred.

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2.3.2.3 Gender

No gender effect on pharmacokinetics of ferumoxytol was observed. In the study 7228-01, the mean volume of distribution (Vd) was 25% smaller (2.1 ± 0.4 L for female subjects and 2.7 ± 0.5 mL/kg for male subjects) and CL was 22% slower in female subjects than in male subjects (96.4 ± 13.2 mL/hr for female subjects and 123 ± 24.6 mL/hr for male subjects). However, normalization based on weight eliminated these differences.

Furthermore, a subgroup analysis of the integrated clinical data showed no significant difference in pharmacodynamic parameters, i.e., increase of hemoglobin from baseline, by gender (Refer to Table 9).

2.3.2.4 Race

The preliminary comparison showed that there was no significant difference in PK of ferumoxytol between African-American and Caucasian (See the Table 10 below; the data come from study 62745-9). Furthermore, a subgroup analysis of the integrated clinical data showed no significant difference in pharmacodynamic parameters, i.e., increase of hemoglobin from baseline, by race (Refer to Table 9 above).

Table 10. Comparison of pharmacokinetic parameters of ferumoxytol after administration of 2x510 mg among different ethnic groups.

Race	African-American	Caucasian	Asian	Hispanic
n	47	8	1	3
Age (Year)	29.4 ± 7.57	33.1 ± 9.3	43	39.7 ± 4.7
Height (Cm)	172 ± 10	173 ± 8.3	163	168 ± 4.4
Weight (Kg)	76.2 ± 12.7	79.3 ± 15.4	65.6	78 ± 4.7
V1 (L)	2.64 ± 0.43	2.86 ± 0.39	2.77	2.53 ± 0.18
Vmax (mg Fe/Hr)	14.35 ± 1.28	14.5 ± 0.87	15.8	13.93 ± 1.69
Km (mg Fe)	209 ± 19.3	207 ± 18.4	199	190.3 ± 4.93
V2 (L)	0.49 ± 0.15	0.55 ± 0.24	0.643	0.277 ± 0.087
Q (L/hr)	0.025 ± 0.017	0.034 ± 0.019	0.0275	0.031 ± 0.007

V1 represents the volume of distribution of central compartment.

Vmax represents the maximum elimination rate from the plasma (mg/hr)

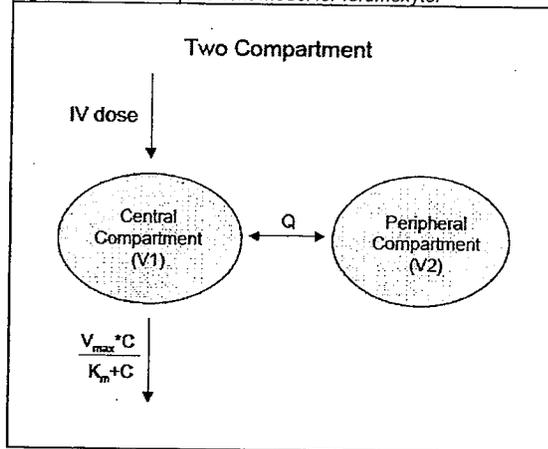
Km represents the plasma concentration at half maximum rate of elimination from the plasma.

V2 represents the volume of distribution of the peripheral compartment.

Q represents the distribution clearance between the central and peripheral compartment.

See the following diagram for the model describing the pharmacokinetics of ferumoxitol.

Figure 13. Two compartment model for ferumoxitol



2.3.2.5 Hepatic impairment

No study has been conducted.

2.3.2.6 What pregnancy and lactation use information is there in the application?

There are no adequate and well-controlled studies in pregnant women.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

No specific studies or analyses were designed to evaluate the effects of factors such as other drugs (drug-drug-interaction), herbal products, diet, smoking or alcohol use on the PK or PD of ferumoxitol.

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Not applicable

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

Bioavailability is not an issue for ferumoxitol as the formulation is for IV injection and the formulation was not changed during the development of ferumoxitol.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Spin-lattice relaxation time (T1) was used to quantify ferumoxytol concentrations in plasma or serum samples. The methods were developed and validated by AMAG Pharmaceuticals, Inc. using a time domain benchtop nuclear magnetic resonance (NMR) spectrometer with an applied field of \sim Tesla (20 μ m). Three different instruments were used, an IBM PC-20 NMR spectrometer, a Bruker PC-120 NMR spectrometer or a Bruker Minispec mq \sim NMR analyzer. In each of these methods, the high correlation of the fit for ferumoxytol concentration versus 1/T1 indicated that relaxation time testing was a valid method for measuring ferumoxytol in plasma or serum samples.

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Three validation results for the NMR methods are reported in Reports RD-1275 (human plasma), RD-1276 (human serum), and RD-7228-001 (human plasma). The validation results are summarized in the table below.

Table 11. Summary of the analytical method validation.

Parameter	Report Number		
	RD-1275	RD-1276	RD-7228-001
Regression Coefficient	0.9997	0.9998	0.993
Accuracy (% \pm SD or % range)	100 \pm 3.1	102 \pm 6.4	97-103
Accuracy Range (μ g/mL)	2.91-117.40	2.79-167.36	NR
Precision (%)	0.5-5.5	0.5-16.5	NR
LOQ or LLOQ (μ g/mL) ^a	5.83	11.16	6.0

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Abbreviations: LLOQ=lower limit of quantitation; LOQ=limit of quantitation; NR=not reported; SD=standard deviation.

^a LOQ for RD-1275 and RD-1276; LLOQ for RD-7228-001.

For the determination of ferumoxytol in human plasma samples (Report RD-1275) using the IBM PC-120 NMR spectrometer, the ferumoxytol concentration versus 1/T1 concentration was fit to a line using a cubic equation with a regression coefficient (R²) of 0.9997 (See the table below). Evaluation of the recovery of spiked samples indicated that the T1 curve fit was accurate between 2.91 and 117.40 μ g/mL; the mean recoveries were accurate (100 \pm 3.1%) between these limits with a precision of T1 measurements between 0.5% to 5.5%. The limit of quantitation (LOQ) of the assay was 5.83 μ g/mL.

For the determination of ferumoxytol in human serum samples (Report RD-1276) using the Bruker PC-120 NMR spectrometer, the ferumoxytol concentration versus 1/T1 concentration was fit to a line using a cubic equation with an R²=0.9998 (Table 2). Evaluation of the recovery of spiked samples indicated that the T1 curve fit was accurate between 2.79 and 167.36 μ g/mL; the mean recoveries were accurate (102 \pm 6.4%) between these limits with a precision of T1 measurements between 0.5% to 16.5%. The LOQ of the assay was 11.16 μ g/mL.

In another validation protocol for the determination of ferumoxytol in human plasma samples using the Bruker Minispec mq \sim NMR Analyzer, the concentration-response relationship was determined to be linear (R²=0.993) and recovery of spiked samples ranged between 97% to 103% with a percent coefficient of variation (%CV) at each concentration of less than 3%. The lower limit of quantitation (LLOQ) for the assay was determined to be 6 μ g/mL. In addition, ferumoxytol was spiked into six different plasma samples at the LLOQ level and the recovery of ferumoxytol was 82% to 87% in each sample.

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Studies 7228-01, 62,745-9, and Study 62,745-2 used method 7228-001, RD1275, and RD1276, respectively, for assay of ferumoxytol.

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ON ORIGINAL**

3 Detailed Labeling Recommendations

Only relevant clinical pharmacology sections are included. Double Underlines indicate content that was added by the agency and ~~strikethroughs~~ indicate content taken out by the agency.

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21 Page(s) Withheld

 Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

4.2 Individual study review

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Title of study: A Phase I Clinical Investigation of Code 7228 (Amendment 1)

Clinical Phase: I

b(4)

Investigator(s): M. Shenouda, MD

Study Centers: There was one study center: Neptune Clinical Research Center, Neptune, NJ

Dates of Study: 09 June 1999 through 10 August 1999

Date of report: 21 November 2007

Objectives:

- To evaluate the safety of ferumoxytol (previously known as Code 7228) at increasing dose levels through an analysis of changes pre-and post-administration in blood chemistry, urinalysis, vital signs, results of physical examinations and electrocardiograms (ECGs), and by the incidence of adverse events (Part 1 of study).
- To evaluate the pharmacokinetics of the drug by taking blood samples at multiple timepoints to determine blood clearance by magnetic resonance (MR) relaxivity measurements (Parts 1 and 2 of study).
- To evaluate the safety of ferumoxytol at various rates of administration at a dose determined from Part 1 (Part 2 of study).
- To evaluate ferumoxytol for MR imaging of lymph nodes and blood vessels (Part 3 of study).

Methodology:

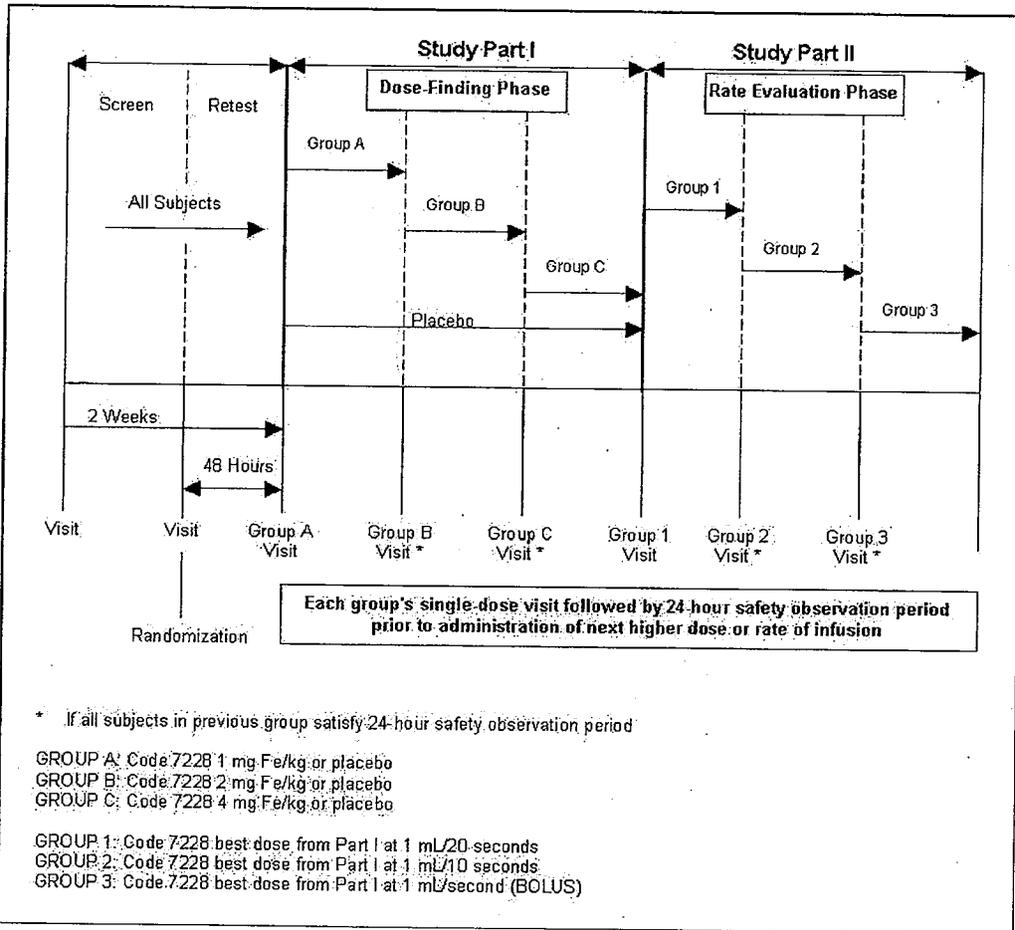
A randomized, double-blind, placebo-controlled, ascending-dose, three-part study.

Thirty subjects total were to be enrolled in Part 1 (4 males and 4 females at each dose, plus 1 male and female to receive placebo during each dosing sequence for the active treatments [ie, 24 active drug, 6 placebo]). Only 10 subjects were to be enrolled in each dose group (5 males, 5 females); no additional subjects were enrolled until a full safety review could be conducted to evaluate the safety and tolerability of ferumoxytol at the previous dose.

In Part 2, nine newly enrolled subjects were given one dose of the highest dose from Part 1 of the study at rates of either 1 mL/20 seconds, 1 mL/10 seconds, or 1 mL/second, depending on order of study entry (first three subjects received dose at the first administration rate, second three subjects received dose at the second administration rate, etc). Part 2 was not randomized or placebo controlled.

In Part 3, two subjects from Part 2 underwent MR imaging at 24 hours to determine lymph node uptake of the drug.

Two additional subjects were enrolled and had MR imaging immediately after administration to evaluate ferumoxytol for visualization of blood vessels.



Number of Subjects: Ferumoxytol: Male 19, Female 16, Total 35 Placebo: Male 3, Female 3, Total 6.

Characteristic	Number of Subjects				Total (N=41) n (%)
	Placebo (N=6)	1 mg Fe/kg (N=8)	2 mg Fe/kg (N=8)	4 mg Fe/kg ^a (N=19)	
Sex					
Male	3	4	4	11	22 (53.7)
Female	3	4	4	8	19 (46.3)
Race					
White	1	2	2	3	8 (19.5)
Black	5	6	5	10	26 (63.4)
Hispanic	0	0	1	6	7 (17.1)
Age, yrs					
Mean±SD	34.0±7.1	35.3±11.6	31.6±6.1	33.5±6.8	33.5±7.7
Range	22 - 41	24 - 58	24 - 43	20 - 50	20 - 58
Height, cm					
Mean±SD	170.2±8.6	173.8±9.9	171.6±8.2	170.3±11.1	171.2±9.8
Range	160.0 - 179.0	157.5 - 187.0	156.0 - 179.0	153.0 - 189.0	153.0 - 189.0
Weight, kg					
Mean±SD	78.3±13.8	85.3±16.6	76.2±14.5	79.1±15.6	79.6±15.1
Range	65.5 - 95.5	64.0 - 115.0	59.0 - 96.5	46.5 - 105.0	46.5 - 115.0

a. The 4 mg Fe/kg dose group includes all subjects receiving 4 mg/kg of ferumoxytol at a dose rate of 2 mL/min (N=8), 1 mL/20 sec (N=3), 1 mL/10 sec (N=3), and 1 mL/sec (N=5).

Abbreviations: cm = centimeter(s); kg = kilogram(s); SD = standard deviation; yr = years.

Diagnosis and criteria for inclusion:

Inclusion criteria:

- Male or female subjects, 18 to 60 years old, in general good health.
- Provided signed, dated, informed consent.

Exclusion criteria:

- Pregnant or lactating women. Women of childbearing potential were required to have a negative urine or serum (human chorionic gonadotropin; β -hCG) pregnancy test or documented history of tubal ligation, hysterectomy, or menopause prior to their inclusion in the study.
- Women of childbearing potential unwilling to use an adequate form of contraception during the course of the study.
- Evidence of organ dysfunction or any clinically significant deviation from normal in the physical, ECG, or clinical laboratory examinations.
- Known allergy to dextran or iron-containing compounds (including multivitamins or iron supplements).
- HIV-positive subjects.
- History of cardiovascular, hepatic, hematopoietic, gastrointestinal, neuromuscular, renal, or metabolic dysfunction.
- Sitting blood pressure (BP) <100/70 mm Hg and/or a radial pulse rate <60 bpm; or a sitting BP >140/90 mm Hg and/or a radial pulse rate >80 bpm.
- Screening serum ferritin levels >120 ng/ml.
- Use of any drugs, including over-the-counter (OTC) preparations and vitamins, within 1 week prior to study enrollment.
- Participation in any other clinical trial with another investigational drug, or use of an investigational drug within the 60 days prior to inclusion in the study.
- History of alcohol or drug abuse within 6 months of study entry.
- Screening laboratory results outside of the normal range limits that were considered to be clinically significant upon review by the investigator.
- Current medical status that, in the investigator's opinion, precluded the subject's participation in the study (eg, multiple drug sensitivities; history of previous reactions to contrast media; known allergies, such as bronchial asthma; other hypersensitivities and underlying immune disorders, autoimmunity, or immunodeficiencies that predispose to specific or nonspecific mediator release).

Dosage and Administration:

- Part 1 of Study: Ferumoxytol at escalating doses (1, 2, and 4 mg Fe/kg) and matching doses of placebo (normal sterile saline) were administered intravenously. Ferumoxytol was formulated at 30 mg Fe/mL with mannitol (44 mg/mL).
- Part 2 of Study: Ferumoxytol at the highest dose from Part 1 at administration rates of 1 mL/20 seconds, 1 mL/10 seconds, or 1 mL/second (bolus dose)
- Part 3 of Study: Ferumoxytol at a dose of 4 mg Fe/kg in two subjects who had MR imaging of blood vessels, and in two subjects from Part 2 who had MR imaging for lymph node evaluation.

Duration of Treatment: Each subject received a single dose of ferumoxytol or placebo

Criteria for evaluation:

Efficacy:

Evaluation of pharmacokinetic (PK) parameters for ferumoxytol included area under the plasma concentration-time curve (AUC) from time 0 to infinity ($AUC_{0-\infty}$), time 0 to 24 hours (AUC_{0-24}), time 0 to 8 hours (AUC_{0-8}), and time 0 to the time of the last quantifiable plasma concentration ($AUC_{0-tlast}$); clearance (CL); maximum concentration (C_{max}); time of maximum concentration (t_{max}); terminal elimination rate constant (λ_z); half-life ($t_{1/2}$); and volume of distribution (V_z).

Magnetic resonance imaging (MRI) included the evaluation of lymph node uptake 24 hours after ferumoxytol administration and visualization of blood vessels immediately after administration.

Safety:

Adverse event monitoring, changes in clinical laboratory evaluations, ECG parameters, physical examination, vital signs, oxygen saturation (SO_2), and injection site monitoring.

Statistical methods:

Pharmacokinetic parameters were estimated using noncompartmental analysis and WinNonlin® Professional, Version 5.1.1 (Pharsight® Corporation, Mountain View, CA). Additional analyses were performed on these PK parameter estimates using SAS®, Version 8.2 (SAS Corporation, Cary, NC) to assess the effects of gender,

dose and administration rate. Both parametric (analysis of variance) and nonparametric (Kruskal-Wallis) methods were used.

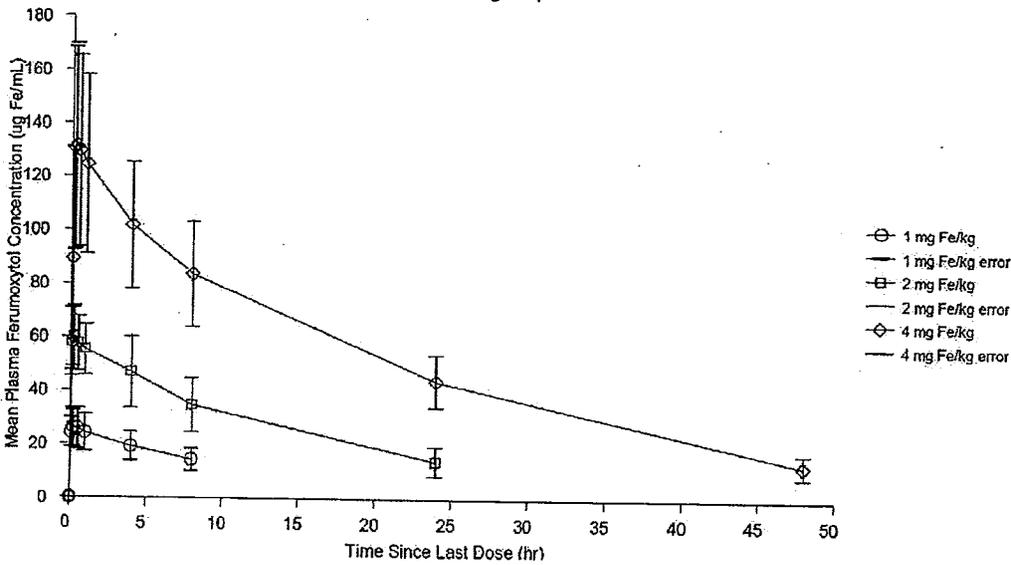
Where applicable, the Bonferroni method was used to adjust for multiple comparisons when testing pairwise differences.

Statistical analyses of clinical data were performed using SAS®, Version 9.1. Continuous variables were described with descriptive statistics.

Publication (reference): Landry R, Jacobs PM, Davis R, Shenouda M, Bolton WK. Pharmacokinetic study of ferumoxytol: a new iron replacement therapy in normal subjects and hemodialysis patients. *Am J Nephrol.* 2005;25(4):400-10

Pharmacokinetic results:

Statistically significant increases in $t_{1/2}$ and dose normalized $AUC_{0-\infty}$ were observed with increasing dose. Corresponding to the $AUC_{0-\infty}$ finding, CL was significantly lower at higher doses. Volume of distribution values decreased with increasing dose, however, weight-normalized V_z diminished these differences. Dose normalized C_{max} values were not different between dose groups.

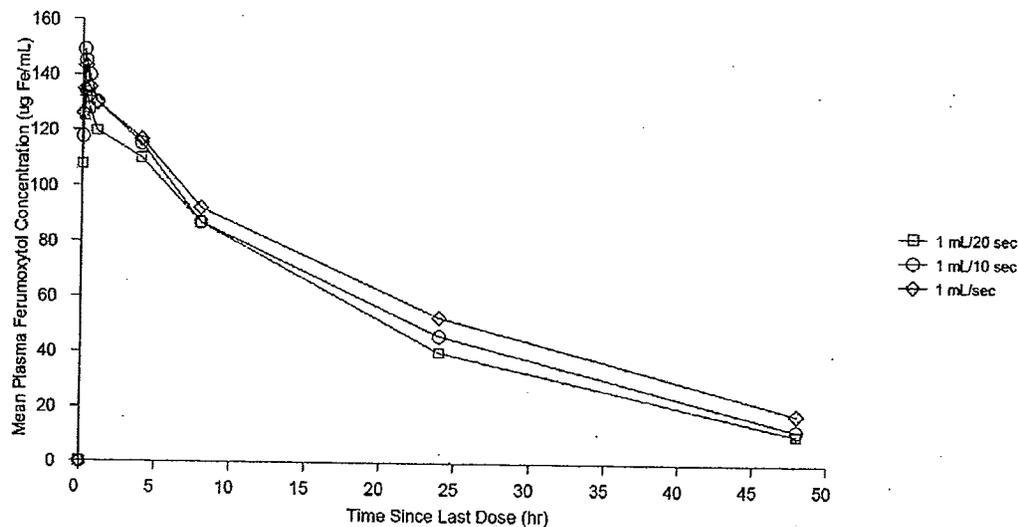


Mean (SD) Values for PK Parameters by Ferumoxytol Dose Group

PK Parameter ^a	Dose Group		
	1 mg Fe/kg	2 mg Fe/kg	4 mg Fe/kg
	(N=8)	(N=8)	(N=8)
λ_z (hr ⁻¹)	0.0744 (0.0172)	0.062 (0.0078)	0.0487 (0.0058)
$t_{1/2}$ (hr)	9.72 (2.01)	11.4 (1.55)	14.4 (1.74)
t_{last} (hr)	8.0 (8.0-24.0) ^b	24.0 (23.9-45.0) ^b	49.1 (45.7-69.1) ^b
C_{last} (µg/mL)	12.7 (3.68)	11.7 (3.61)	11.1 (3.86)
t_{max} (hr)	0.167 (0.083-0.500) ^b	0.167 (0.083-0.250) ^b	0.250 (0.083-1.00) ^b
C_{max} (µg/mL)	27.0 (7.70)	62.2 (12.0)	134 (36.1)
$C_{max}/Dose$	27.0 (7.70)	31.1 (6.00)	33.5 (9.03)
[(µg/mL)/(mg Fe/kg)]			
AUC ₀₋₈ (µg·hr/mL)	156 (44.6)	371 (87.2)	830 (199)
AUC _{0-∞} (µg·hr/mL)	365 (128)	996 (313)	2800 (625)
AUC _{0-8}/Dose}	156 (44.6)	186 (43.6)	208 (49.7)
[(µg·hr/mL)/(mg Fe/kg)]			
AUC _{0-∞}/Dose}	365 (128)	498 (157)	700 (156)
[(µg·hr/mL)/(mg Fe/kg)]			
Extrapolated AUC (%)	50.9 (13.6)	20.3 (6.72)	8.62 (3.67)
CL (mL/hr)	265 (118)	164 (55.5)	114 (15.2)
CL/weight (mL/hr/kg)	3.15 (1.52)	2.18 (0.660)	1.49 (0.321)
V_z (mL)	3450 (808)	2620 (674)	2380 (442)
$V_z/weight$ (mL/kg)	41.5 (11.8)	34.8 (7.92)	31.1 (8.38)

a. See Table 1 for an explanation of abbreviations and specialist terms.
b. Values presented as median (range).

The PK parameters for ferumoxytol at a dose of 4 mg Fe/kg were unaffected by the administration rate.



PK Parameter	Dose Group		
	1 mL/20 Sec	1 mL/10 Sec	1 mL/Sec
	(N=3)	(N=3)	(N=3)
λ_z (hr ⁻¹)	0.0465 (0.0097)	0.0486 (0.0071)	0.0434 (0.0031)
$t_{1/2}$ (hr)	15.3 (3.19)	14.5 (2.18)	16.0 (1.20)
t_{last} (hr)	48.0 (47.7-72.0) ^b	49.0 (47.1-49.6) ^b	49.0 (24.0-72.0) ^b
C_{last} (µg/mL)	10.4 (2.02)	12.5 (4.21)	25.4 (26.6)
t_{max} (hr)	0.250 (0.250-0.250) ^b	0.167 (0.0833-0.250) ^b	0.250 (0.250-0.333) ^b
C_{max} (µg/mL)	134 (26.4)	150 (47.4)	143 (35.6)
AUC ₀₋₂₄ (µg·hr/mL)	1870 (343)	2000 (683)	2070 (497)
AUC _{0-∞} (µg·hr/mL)	2780 (328)	2980 (1030)	3350 (926)
Extrapolated AUC (%)	8.23 (1.85)	8.99 (2.97)	16.7 (15.3)
CL (mL/hr)	119 (37.1)	119 (28.7)	82.7 (9.11)
CL/weight (mL/hr/kg)	1.45 (0.165)	1.44 (0.435)	1.27 (0.404)
V_z (mL)	2650 (979)	2460 (499)	1920 (307)
V_z /weight (mL/kg)	32.5 (9.03)	30.0 (9.36)	29.0 (7.80)

a. See Table 1 for an explanation of abbreviations and specialist terms.

b. Values presented as median (range).

Gender difference:

Upon combining data from all of the 4 mg Fe/kg administration rate groups (Part 1 and Part 2), statistically significant differences in C_{max} , V_z , and CL were detected between men and women. Male subjects, on average, had a lower C_{max} , a higher CL, and a larger V_z . The mean C_{max} for the combined data for the 4 mg Fe/kg dose was about 29% higher among female subjects (157±38 µg/mL) compared with male subjects (122 ± 20 µg/mL). For the subjects receiving the 4 mg Fe/kg dose, $t_{1/2}$ differed by less than 6% between genders (14.4±2.1 hr for females and 15.3±1.8 hr for male subjects). Mean V_z was 25% smaller and CL was 22% slower in female subjects than in male subjects, but weight normalization decreased the differences to about 14% for V_z (28.4±9.5 mL/kg for females and 32.9±5.7 mL/kg for males) and 10% for CL (1.36±0.36 mL/hr/kg for females and 1.51±0.27 mL/hr/kg for males). In general, males had larger V_z and faster CL than females in all dose groups.

Magnetic resonance imaging effects:

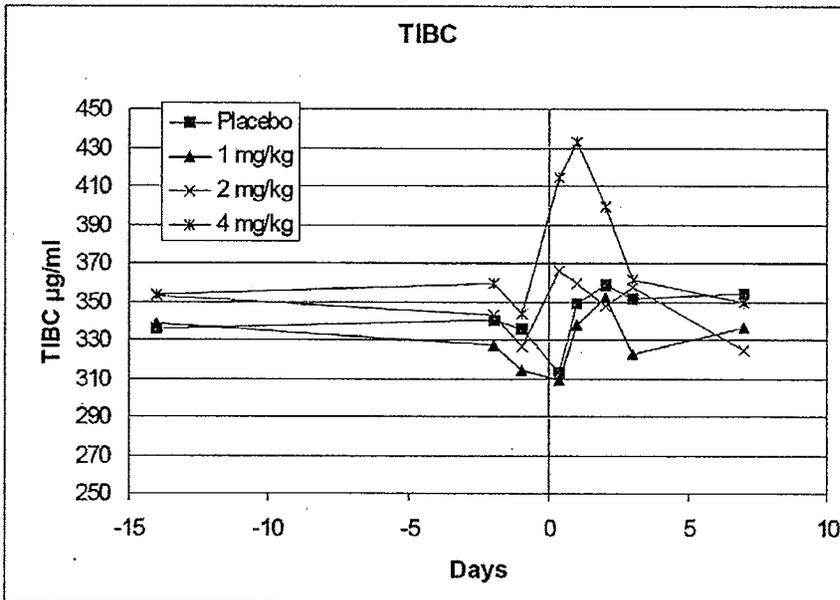
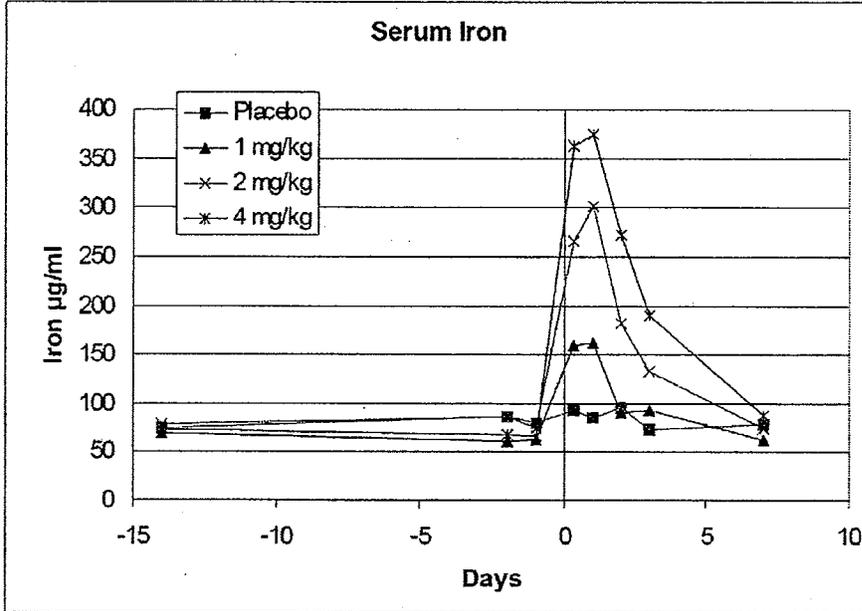
Uptake of ferumoxytol by lymph nodes was seen at 24 hours after administration. On T2 star sequence (T2*) images, the lymph nodes showed a significant loss of signal intensity in two subjects. In two additional subjects who had imaging immediately following ferumoxytol administration, visualization of arterial and venous anatomy in the chest and abdomen was scored better than seen on the unenhanced images.

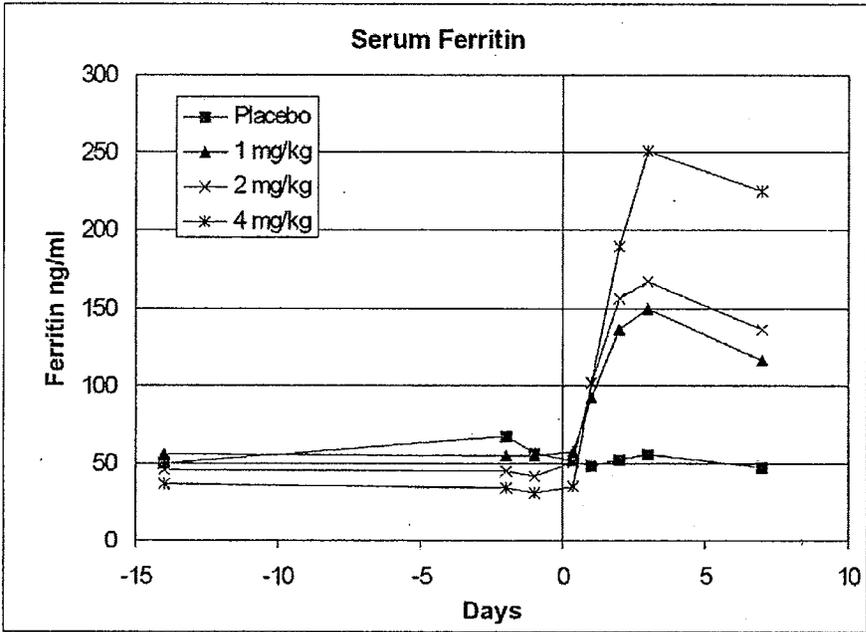
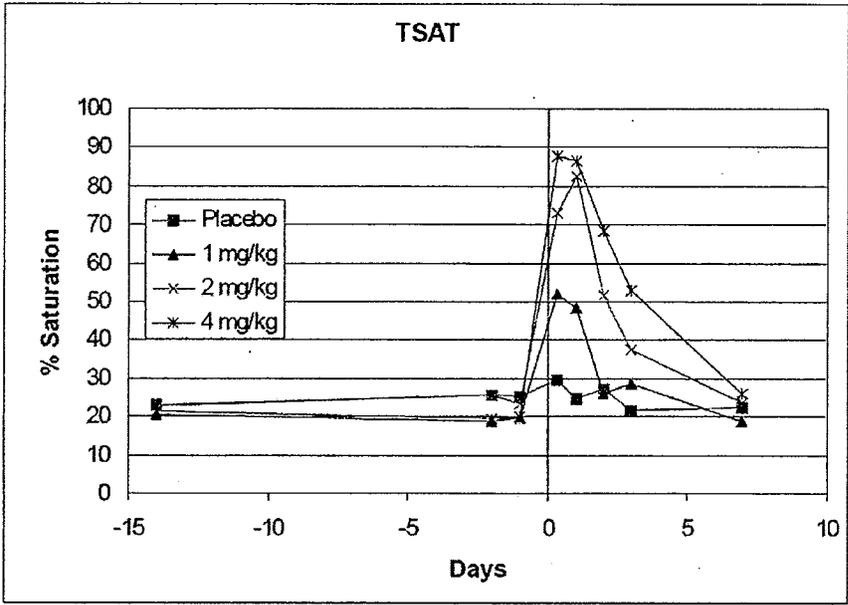
Safety Results:

Treatment-emergent adverse events were reported in two of six subjects who received placebo and six of 35 subjects who received ferumoxytol with only one event (metallic taste) reported as remotely related to ferumoxytol administration. There were no serious adverse events reported during the study. There were three subjects who had pre-existing adverse events that continued following administration of ferumoxytol. One subject had a headache due to caffeine withdrawal that started 5.5 hours before dosing and continued for 24 hours, one subject had a tension headache that began 8 hours prior to dosing and continued for 9.5 hours, and one subject developed a secondary viral upper respiratory infection (cough, myalgia, nasal stuffiness, and a sore throat) 1.5 hours prior to dosing that lasted for 16 days. Although all treated subjects exhibited isolated abnormal laboratory values (compared to the normal ranges) at some time point during the study, no consistent, clinically relevant, or unexpected changes were observed in clinical laboratory, vital signs, or ECG parameters.

As expected, serum iron analysis revealed marked rises in serum iron in a dose-dependent manner, with unbound iron binding capacity functioning as an inverse to serum iron. The percent saturation of transferrin

tended to mirror the serum iron results, rising sharply following dose administration. Ferritin began to rise at Day 1, reflecting some metabolism of the agent, peaked at Day 3, and fell slowly back toward Baseline.





Parameter/ Treatment group ^a	N	Percent Changes from Baseline			
		>40% to 60% Change		>60% Change	
		Increase n (%)	Decrease n (%)	Increase n (%)	Decrease n (%)
% saturation					
Placebo at 2 mL/min	6	2 (33.3)	1 (16.7)	0 (0.0)	0 (0.0)
1 mg/kg at 2 mL/min	8	0 (0.0)	0 (0.0)	8 (100.0)	1 (12.5)
2 mg/kg at 2 mL/min	8	0 (0.0)	1 (12.5)	8 (100.0)	0 (0.0)
4 mg Fe/kg (all doses)	19	0 (0.0)	0 (0.0)	19 (100.0)	0 (0.0)
All Active Doses	35	0 (0.0)	1 (2.9)	35 (100.0)	1 (2.9)
Ferritin					
Placebo at 2 mL/min	6	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1 mg/kg at 2 mL/min	8	1 (12.5)	0 (0.0)	7 (87.5)	0 (0.0)
2 mg/kg at 2 mL/min	8	0 (0.0)	0 (0.0)	8 (100.0)	0 (0.0)
4 mg Fe/kg (all doses)	19	0 (0.0)	0 (0.0)	19 (100.0)	0 (0.0)
All Active Doses	35	1 (2.9)	0 (0.0)	34 (97.1)	0 (0.0)
Iron					
Placebo at 2 mL/min	6	2 (33.3)	1 (16.7)	1 (16.7)	0 (0.0)
1 mg/kg at 2 mL/min	8	0 (0.0)	1 (12.5)	8 (100.0)	0 (0.0)
2 mg/kg at 2 mL/min	8	0 (0.0)	1 (12.5)	8 (100.0)	1 (12.5)
4 mg Fe/kg (all doses)	19	0 (0.0)	0 (0.0)	19 (100.0)	0 (0.0)
All Active Doses	35	0 (0.0)	2 (5.7)	35 (100.0)	1 (2.9)
TIBC					
Placebo at 2 mL/min	6	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1 mg/kg at 2 mL/min	8	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2 mg/kg at 2 mL/min	8	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4 mg Fe/kg (all doses)	19	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)
All Active Doses	35	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)

a. The 4 mg Fe/kg dose group includes all subjects receiving 4 mg/kg of ferumoxytol at a dose rate of 2 mL/min (N=8), 1 mL/20 sec (N=3), 1 mL/10 sec (N=3), and 1 mL/sec (N=5).
Abbreviations: TIBC = total iron binding capacity.

Overall, there were no differences between 2 weeks pre-dose, 2 days pre-dose, and 1 day pre-dose in the between-dose ANOVA analysis in serum iron, total iron binding capacity (TIBC), and ferritin. Following dose administration, however, differences were notable. At 8 hours, serum iron and TIBC varied significantly by dose, and all varied significantly by dose at Days 1, 2, and 3. By Day 7, only ferritin varied by dose. ANOVA by time showed no variation for the placebo and significant variation by time for all three dose levels, as expected.

Conclusions:

- Intravenous ferumoxytol demonstrated dose-dependent pharmacokinetics. The volume of distribution approximated plasma volume at all doses.
- The Values of Clearance and volume of distribution of iron oxide in ferumoxytol appeared larger in males compared to female. The body weight appeared to be a covariate. Dose adjustment is not necessary as the difference is 22 – 25 %.
- The rate of administration had no effect on ferumoxytol PK parameters.
- Serum iron parameters appeared to be changed after ferumoxytol administration with dose dependent manner.

62745-2 (Patients CKD-5D)

Protocol Number: Protocol 62,745-2

Title of Study: A Phase I Open-Label, Rate Administration, Pharmacokinetic Study of the Safety of Code 7228 as an Iron Replacement Therapy in Chronic Hemodialysis Patients Who Are Receiving Supplemental EPO Therapy

Principal Investigator: W. Kline Bolton, MD

Study center(s): This was a single center study in the United States (US) at the University of Virginia Health System, Charlottesville, VA 22908.

Publications (reference): Landry, R., et al., Pharmacokinetic study of ferumoxytol: a new iron replacement therapy in normal subjects and hemodialysis patients. *Am J Nephrol.*, 2005. 25(4): p. 400-10.

Studied period (years):

Date first subject enrolled: 26 September 2001

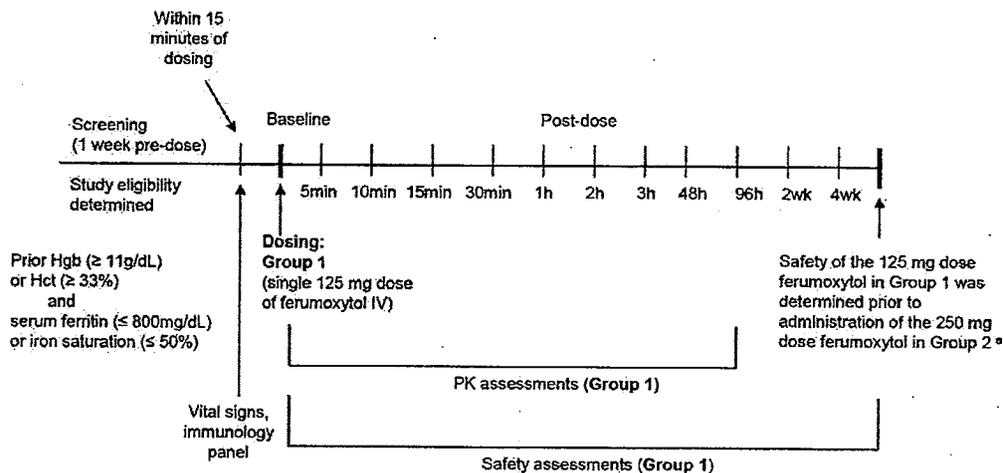
Date last subject completed: 10 April 2002

Date of the report: 25 September 2007

Phase of development: I

Objectives: The objective of this study was to evaluate the safety and pharmacokinetics (PK) of two dose levels (125 and 250 mg) of ferumoxytol (referred to as Code 7228 in the protocol and supporting documents) in subjects with chronic kidney disease (CKD) stage 5D who were on hemodialysis and receiving supplemental erythropoietin therapy.

Methodology: This was a Phase I, open-label, uncontrolled, single center, PK and safety study of ferumoxytol in subjects with CKD stage 5D who were on hemodialysis and receiving supplemental erythropoietin therapy.



a. Once the safety of the 125 mg dose (Group 1) of ferumoxytol was determined, new subjects who met criteria for inclusion in the study and were assigned to Group 2 received a single 250 mg dose of ferumoxytol. Pre- and post-dose PK and safety assessments shown in Figure 1 were repeated for the higher dose group.

The study consisted of a Screening period and an open-label treatment period. Following the Screening period, eligible subjects were assigned to one of two ferumoxytol dose groups and received a single dose of either 125 mg (Group 1) or 250 mg (Group 2) ferumoxytol administered intravenously (IV); upon completion of the enrollment and assessment of subjects in the 125 mg group (Group 1), additional subjects were then enrolled in the 250 mg group (Group 2).

Screening/Baseline Period: Clinical laboratory tests were performed 1 week prior to dosing to determine eligibility for inclusion in the study. Subjects were required to have a hemoglobin (Hgb) measurement that satisfied the study entry criteria of ≥ 11 g/dL, and/or a hematocrit (Hct) of $\geq 33\%$. An iron saturation of $\leq 50\%$ and/or a serum ferritin of ≤ 800 ng/dL were also required for entry into the study. The screening procedures also included vital sign measurements and physical examination, including height and weight (including post-dialysis weight). A complete medical history that included a review of concurrent illnesses and concomitant medications was performed at Screening and again within 3 days of dosing.

Open-label Treatment Period: The first 10 subjects enrolled were assigned to Group 1 and 4 received a single 125 mg dose of open-label ferumoxytol administered over 5 minutes. Safety assessments for all Group 1 subjects were performed prior to administration of a single 250 mg dose of ferumoxytol to Group 2 subjects. In both dose groups, ferumoxytol was administered within 30 minutes after the start of dialysis. The duration of the study for each subject in the two ferumoxytol dose groups was 4 weeks.

Pharmacokinetic evaluations: Blood samples were collected from each subject in both ferumoxytol dose groups for T1 and T2 relaxivity measurements at the following times during hemodialysis: within 15 minutes prior to dosing, and then at 5, 10, 15, 30, 60, 120, and 180 minutes post-dose over the dialysis session. Samples were also collected at 48 and 96 hours post-dose when subjects returned for their subsequent hemodialysis session. Plasma concentrations of ferumoxytol ($\mu\text{g/mL}$) were then determined from the plasma magnetic resonance relaxation time measurements. PK studies of ferumoxytol included area under the curve (AUC), maximum concentration (C_{max}), blood clearance, and volume of distribution.

Safety evaluations:

- Physical examinations: A complete physical examination was performed at Screening and at study completion, 4 weeks post-dosing.
- Clinical laboratory evaluations (hematology, clinical chemistry, iron panel, clotting function panel, and immunology panel): With the exception of the immunology panel, samples were collected at Screening, at the next dialysis session, and at 2 weeks and 4 weeks post-dose. Samples for immunology panel tests were collected within 15 minutes prior to dosing and at 1 hour and 3 hours post-dose. All blood samples for clinical lab tests were drawn prior to dialysis.
- Vital signs: Measurements were performed 1 week prior to dosing, within 15 minutes prior to dosing (Baseline), and at 15 minutes, 30 minutes, 1 hour, 2 hours, and 3 hours post-dose.
- Adverse events (AEs) were monitored throughout the duration of the study.

Number of subjects (planned and analyzed):

A total of 20 subjects were planned for enrollment, with 10 subjects assigned to each of the two ferumoxytol dose groups.

- 125 mg dose group: 10 subjects were enrolled and analyzed
- 250 mg dose group: 10 subjects were enrolled and analyzed

Diagnosis and main criteria for inclusion:

For inclusion into this study, subjects were required to meet the following inclusion criteria:

- 18 years of age or older
- Have given written informed consent
- Undergoing chronic hemodialysis and receiving supplemental erythropoietin therapy
- Have a Hgb measurement that satisfied the entry criteria of ≥ 11 g/dL and/or a Hct of $\geq 33\%$, plus TSAT of $\leq 50\%$ and/or a serum ferritin of ≤ 800 ng/dL

Test product, dose and mode of administration, lot number:

- Ferumoxytol (Code 7228): 125 mg and 250 mg administered IV
- Lot #: 01051501

Duration of treatment:

The duration of the study for each subject in the two ferumoxytol dose groups was 4 weeks.

Reference therapy, dose and mode of administration, lot number:

This was an uncontrolled study; no reference product was included.

Criteria for evaluation:

Efficacy: This was a PK and safety study of ferumoxytol in subjects with CKD on hemodialysis. No efficacy analyses were planned.

Pharmacokinetics: Pharmacokinetic parameters evaluated during the study included AUC, C_{max}, blood clearance, and volume of distribution.

Safety: The safety of ferumoxytol was assessed on the basis of AEs, clinical laboratory tests (hematology, clinical chemistry, iron panel, clotting function panel, and immunology panel), vital signs (blood pressure, heart rate, respiration rate, and temperature), and physical examinations (including height, weight, and post-dialysis weight).

Statistical methods:

Pharmacokinetics: Individual and mean plasma ferumoxytol concentrations and central volume of distribution were calculated. A standard non-compartmental PK analysis was not performed for this study as plasma ferumoxytol concentrations in blood samples collected from subjects in both treatment groups at various timepoints, including 48 and 96 hours post-dose, were below the limit of quantitation. In addition, the terminal elimination rates could not be calculated because plasma samples were not collected between 3 and 48 hours post-dose.

Safety: Adverse events were summarized by system organ class and preferred term for each dose group. The number of events and the number and percentage of subjects with events were categorized by time of occurrence relative to dosing, relationship to dose administration, and intensity. Those AEs resulting in discontinuation of study medication were also summarized. Serious adverse events (SAEs) were summarized by system organ class and preferred term for each dose group. The number of SAEs and the number and percentage of subjects with such events were categorized by relationship to study medication and displayed by system organ class for each dose group.

Laboratory values and absolute change from pre-dose in laboratory values were summarized by visit and by dose group. Descriptive statistics (N, mean, SD, minimum, 25th percentile, median, 75th percentile, and maximum) were displayed for the distributions of each of the laboratory measures. Laboratory data (clinical chemistry, hematology excluding differentials, and iron panel) were classified into low, normal, or high categories relative to the normal ranges. Shifts in classifications of laboratory values from Baseline were displayed by visit and dose group.

Vital signs and absolute change from Baseline in vital signs were summarized by dose group at the following timepoints post-dose: 15 minutes, 30 minutes, 1 hour, 2 hours, and 3 hours. Descriptive statistics were presented for the distributions of each vital sign measure.

The results of the two physical examinations performed during the study, the first prior to the administration of study medication and the second after all dosing was completed, were summarized by dose group using frequencies and percentages by body system.

Results

In this Phase I, open-label, uncontrolled, single center study, the PK and safety of two single doses of ferumoxytol were compared as an iron replacement therapy in subjects with CKD stage 5D who were on hemodialysis and receiving supplemental erythropoietin therapy. A total of 20 subjects were enrolled in this study at one center in the US, and all 20 subjects completed the dosing regimen (10 subjects in each treatment group).

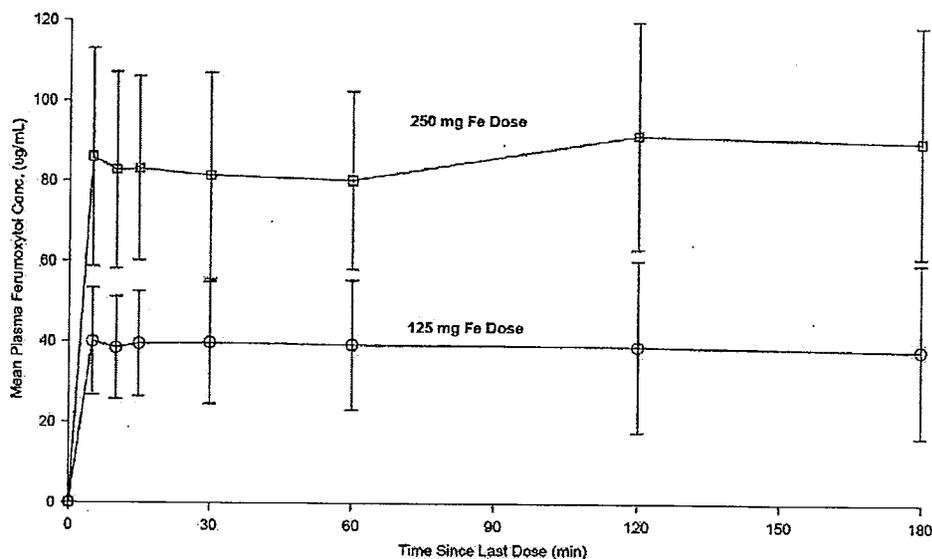
Eight (80%) subjects in the 125 mg dose group and nine (90%) subjects in the 250 mg dose group completed all safety evaluations following dosing with ferumoxytol.

Protocol deviations are as follows: Subject 0201-0107 in Group 1 used a prohibited medication (Ferrlicit) during the study. Subjects 0201-0101 and 0201-0104 in Group 1 and Subject 0201-0112 in Group 2 did not undergo all

safety evaluations as specified by the protocol. Laboratory tests at specific timepoints post-dose were either missed or not done for both Group 1 subjects; for the subject in Group 2, lactate dehydrogenase (LDH) was not obtained at the 48-hour post-dose timepoint.

PHARMACOKINETIC RESULTS:

Analysis of plasma ferumoxytol iron concentrations was performed using samples collected from subjects in both treatment groups immediately prior to dosing and at several timepoints post-dose. Concentrations of plasma ferumoxytol did not decline substantially over the 3-hour hemodialysis period. The mean plasma ferumoxytol concentrations for the 250 mg dose were approximately double those observed for the 125 mg dose, suggesting dose proportionality at these administered doses. Ferumoxytol appeared to be cleared from blood after 48 hours in the 5D CD patients. This suggests that kidneys are not contributing the elimination of ferumoxytol.



SAFETY RESULTS:

The overall incidence of AEs was low and similar between the 125 mg (Group 1) and 250 mg (Group 2) ferumoxytol dose groups. No subject in either treatment group reported an AE prior to dosing with ferumoxytol. Two subjects in Group 1 (bacteremia, vomiting, and wound drainage) and two subjects in Group 2 (feces discolored and transient ischemic attack) reported a total of five AEs. Only one subject in Group 1 experienced an AE (vomiting) considered to be related to study medication. There were no deaths reported during the study. One subject with a history of cerebrovascular accident in Group 2 had an SAE (transient ischemic attack) that was considered to be not related to treatment with ferumoxytol. There were no reports of injection interruptions or permanent discontinuation of study medication due to an AE in either treatment group during the study. Evaluation of laboratory data (absolute values and mean changes over time) did not demonstrate any relevant clinical differences between subjects in either treatment Groups 1 or 2, with the exception of the expected changes in iron-related parameters associated with a response to iron replacement therapy in this study. The number of subjects with shifts in hematology, clinical chemistry, and iron-related parameters from normal values at Baseline to abnormal high or low values at timepoints post-dose was small and did not reveal any clinically meaningful between group differences. Only two subjects, one in each treatment group, had shifts from normal at Baseline to high values post-dosing for any parameter reflecting liver function. Clinically important abnormalities involving laboratory tests were uncommon in both treatment groups during the study. One subject in Group 1, had clinically significant high values at one or more timepoints post-dose for aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyltransferase (GGT), and alkaline phosphatase that were considered by the Investigator to be possibly related to treatment with ferumoxytol. The AST was >2.5x the upper limit of normal (ULN). Other abnormal laboratory values reported during the study were associated with hematology and clotting function. One subject in Group 1 had an increase from Baseline at 1 hour and a decrease from Baseline at 3 hours for PMNs that were considered by the Investigator to be clinically significant; the relationship of the changes in values for PMNs to ferumoxytol was unknown. Prolonged

activated partial thromboplastin time (aPTT) values post-dosing were also considered by the Investigator to be clinically significant for one subject in Group 2 who was taking warfarin as a concomitant medication; the prolonged aPTT values were considered by the Investigator as not related to treatment with ferumoxytol. Changes in vital sign measures from pre-dose showed no clinically meaningful differences during the 3-hour observation period following treatment with ferumoxytol; no important differences between treatment groups were observed at any timepoint post-dose. In both treatment groups, a decrease from Baseline (within 15 minutes prior to dosing) in mean and median values for systolic blood pressure and diastolic blood pressure was observed over the 3-hour observation period post-dosing with ferumoxytol. The observed decreases in blood pressure values were not considered to be related to ferumoxytol, but a consequence of fluid removal during hemodialysis.

In addition, there were no reports of any AEs associated with an increase or decrease in blood pressure during the study.

No between-group differences in physical examination findings were apparent during the study.

CONCLUSION:

The safety results from this study demonstrated that ferumoxytol when administered IV as a single 125 mg or 250 mg dose is well tolerated in subjects with CKD stage 5D on hemodialysis.

Results from the analysis of plasma ferumoxytol iron concentrations suggest dose proportionality at the administered doses of 125 mg and 250 mg elemental iron (Fe) as ferumoxytol.

Concentrations of plasma ferumoxytol did not decline substantially over the 3-hour hemodialysis period. However, ferumoxytol appeared to be cleared from blood after 48 hours in the 5D CD patients. This suggests that ferumoxytol appears to be cleared from plasma and the kidneys are not major eliminating organ.

62745-9 (PK & QT)

**APPEARS THIS WAY
ON ORIGINAL**

Title of Study: A Phase 1 Active- and Placebo-Controlled Study of the Electrocardiogram Effects and Pharmacokinetics of Ferumoxytol in Healthy Men and Women

Principal Investigator: Ronald Goldwater, MD

Study center(s): PAREXEL International, Inc., Baltimore Clinical Pharmacology Research Unit, Harbor Hospital Center, 7th Floor, 3001 South Hanover Street, Baltimore, MD 21225

Publications (reference): None

Studied period: 22 May 2006 to 04 September 2006

Date of the report: 12 October 2006

Phase of development: I

Objectives:

Primary Objectives:

- To define the effect of two doses of 510 mg ferumoxytol administered within 24 hours on QTcI;
- To define the effect of two doses of 510 mg ferumoxytol administered within 24 hours on QT, QTcB, QTcF and heart rate (HR);
- To assess the pharmacokinetics of two doses of 510 mg ferumoxytol administered within 24 hours.

Secondary Objectives:

- To describe the relationship between exposure to ferumoxytol and ECG parameters (QT, QTcI, QTcB, QTcF and HR);
- To assess the safety and tolerability of a suprathreshold regimen of ferumoxytol (2 doses of 510 mg ferumoxytol administered within 24 hours).

Methodology:

Healthy male and female subjects were randomized so that 174 subjects (58 subjects in each treatment group) could complete the study. Each subject received one of three treatment regimens:

Treatment Group 1: moxifloxacin;

Treatment Group 2: ferumoxytol; or

Treatment Group 3: placebo.

A parallel group design was utilized to study a suprathreshold regimen of two 510 mg doses of ferumoxytol in a blinded fashion compared with two doses of placebo. Moxifloxacin, an agent known to increase the QT interval, was given as a positive control.

Screening (within 21 days of Day 0): sign informed consent and HIPAA; information regarding demographics, medical history and medication use collected; screen for entrance criteria; complete physical examination; clinical laboratory tests, including drug screen, testing for HIV, Hepatitis A and Hepatitis B, and a serum pregnancy test (females only); 12-lead ECG; measure supine vital signs									
Procedure	Inpatient						Outpatient		
	Day -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Admission to the Phase 1 Unit	X								
Outpatient Visit							X	X	X
Review Entrance Criteria	X								
Update Medical History	X								
Update Medication Use	X						X	X	X
Physical Examination ¹	X								X
Clinical Laboratory Tests ²	X ³								X ³
Supine Vital Signs ³	X	X	X ⁷	X ⁷					X
12-Lead ECG		X ⁶	X ⁸	X ^{6,8}	X ¹²				X
24-hour Holter Monitoring		X		X					
AE Monitoring ⁴	X	X	X	X	X	X	X	X	X
Study Medication Administration			X ⁹	X ⁹					
PK Sampling			X ¹⁰	X ^{10,11,14}	X ^{12,14}	X ¹³	X ¹³	X ¹³	X ¹³
Discharge from the Phase 1 Unit						X			

1. A brief physical examination on Day -1 and a complete physical examination on Day 7.
 2. CBC, chemistry, clotting function panel, iron panel, urinalysis.
 3. Pulse, blood pressure, respiration rate and temperature were obtained after the subject had been in the supine position for 5 minutes.
 4. Monitored for pre-dose or baseline signs and symptoms or post-dose adverse events.
 5. A serum pregnancy test performed for all females.
 6. The 12-lead ECG was performed prior to the 24 hour Holter monitoring.
 7. 30 minutes (\pm 5 minutes) pre-dose; 5, 10, 15, 20, 30 and 60 minutes post-dose.
 8. Within 1 hour prior to dosing on Day 1, within 15 minutes prior to dosing on Day 2; 15 minutes and 1 hour post-dose on Days 1 and 2
 9. Treatment Groups 2 and 3 were dosed on Day 1. Treatment Groups 1, 2 and 3 were dosed on Day 2.
 10. Pre-dose (within 15 minutes prior to dosing); 5, 10, 15 and 30 minutes post-dose; 1, 4, 8, 12 and 24 hours post-dose (Subjects in Treatment Groups 2 and 3 only.)
 11. This pre-dose sample was taken within 15 minutes prior to administration of the second dose of study medication to ensure that the second dose is given at Time 0, 24 hours after the first dose.
 12. Time 0 (24 hours after dosing on Day 2)
 13. Time 0 = 24 (\pm 1), 48 (\pm 1), 72 (\pm 3), 96 (\pm 3) and 120 (\pm 3) hours after the second dose of study medication. (Subjects in Treatment Groups 2 and 3 only.)
 14. The Day 1, 24 hour and Day 2, Time 0 timepoints designate the same time, so one sample was taken. Likewise, the Day 2, 24 hour and Day 3, Time 0 timepoints designate the same time, so one sample was taken.
- Note: The following procedures were to be performed in the event that a subject withdrew early from the study: update medication use, clinical laboratory tests, 12-lead ECG, complete physical examination, supine vital signs, AE monitoring.

Assessment timepoints were designed to maximize the evaluation of ferumoxytol exposure and to ensure that the potential lag time of ferumoxytol to cause any changes in protein ion channels in cardiac tissue were assessed. To eliminate the potential of heart rate changes influencing the QTc data, an individualized correction for the QT was used (QTcI), as well as Bazett (QTcB) and Fridericia's (QTcF) correction methods. All ECGs were reviewed by three independent cardiologists. A centralized ECG reading lab (eResearch Technology, Inc., Philadelphia, PA), who was blinded to study treatment, was used to read the ECGs, and Joel Morganroth, M.D. reviewed the data and authored the ECG report. Serial blood samples were collected for pharmacokinetic analyses on Day 1 and Day 2 from subjects in Treatments Groups 2 and 3. Ferumoxytol concentrations were determined for Treatment Group 2 using a validated drug-specific nuclear magnetic resonance assay. Ferumoxytol plasma levels in relation to QTcI duration (pharmacodynamic effect) from subjects in Treatment Group 2 were analyzed.

Number of patients (planned and analyzed): 174 planned and analyzed for safety; 58 planned and 57 analyzed for pharmacokinetics.

Diagnosis and main criteria for inclusion: Healthy volunteers; either gender; 18-45 years of age.

Test product, dose and mode of administration, batch number:

Ferumoxytol; two 510 mg doses administered intravenously, one dose each on Day 1 and Day 2; lot numbers 05091301 and 05091501

Duration of treatment: A single dose of ferumoxytol or placebo on Day 1 and Day 2 between 08:00 and 10:20.

Reference therapy, dose and mode of administration, batch number:

Placebo (normal saline); administered intravenously on Day 1 and Day 2; lot number J6C528
Moxifloxacin; 400 mg administered orally on Day 2; lot numbers 5400NL6

Criteria for evaluation:

Pharmacodynamic: A time-matched change from baseline in QTc (corrected for placebo) based on an individual correction method (QTcl) was the primary endpoint of the trial. The formula provided an optimization of QT correction for each individual heart rate as compared to fixed exponent approaches (Bazett and Fridericia). Three independent cardiologists read each ECG. Ferumoxytol plasma levels in relation to QTcl duration (pharmacodynamic effect) from subjects in Treatment Group 2 were analyzed.

Safety: Subjects were monitored for safety from the screening visit until the end of the study on Day 7. These events were classified as adverse events (AEs) as described below. In addition, clinical laboratory tests, vital signs measurements, resting safety 12 lead ECGs, and physical examinations were performed.

Pharmacokinetic: The following pharmacokinetic parameters were to be estimated for each subject in Group 2 (ferumoxytol) from the 0 – 24 hour concentration vs. time data after Day 1 dosing and from the 0 – 120 hour concentration vs. time data after Day 2 dosing: C_{max}, T_{max}, λ_z, t_{1/2}, AUC₀₋₂₄, AUC_{last}, AUC_{inf}, CI, and V_d. All AUC parameters were to be derived using the linear log trapezoidal rule.

Statistical methods: Ferumoxytol plasma concentration vs. time data were analyzed via noncompartmental methods using WinNonlin (version 5.1). All AUC parameters were to be derived using the linear log trapezoidal rule. Plasma concentration and parameter data were listed for each subject. Plasma concentration data were also displayed in tabular and graphical formats. Individual and mean (±SE) plasma concentration vs. time curves were displayed on the log₁₀ and linear scales.

Parameter data were summarized descriptively and displayed in tabular format.

Plasma concentrations of ferumoxytol were summarized with descriptive statistics (N, mean, SD, CV%, median, minimum, and maximum) and tabulated at each time point by treatment group. Mean plasma concentration-time profiles were plotted by treatment on linear and semi-logarithmic scales.

Individual subject plasma concentrations were presented in data listings. Individual subject plasma concentration-time profiles were plotted on linear and semi-logarithmic scales. Concentrations below the quantitation limit (BQL) were treated as zero for descriptive statistics. Scheduled sampling times were used for all pharmacokinetic computations.

Central tendency, time-matched and time-averaged analysis were performed, and outlier effects for heart rate, PR, QRS, QT, QTcl, QTcB, and QTcF intervals were described. The primary endpoint, QTcl, eliminates the effect of heart rate on QT duration. The other QTc fixed exponent methods were provided for historical purposes. Post-dose ECG morphological changes were defined.

Adverse events were summarized by MedDRA system-organ class, MedDRA preferred term, intensity and causality. Number and percentage of subjects who experienced an event and the number of events were tabulated for each system-organ class and preferred term. Adverse events were also tabulated according to intensity and causality. Laboratory data were summarized to show change from baseline and shift relative to normal ranges. Descriptive statistics as well as changes from baseline were also presented by treatment group and visit. Clinically significant laboratory test abnormalities that were considered AEs by the Investigator were presented by treatment group in the AE listing. Vital signs were summarized to show absolute change from baseline. Descriptive statistics as well as changes from baseline were also presented by treatment group and visit. Clinically significant vital sign findings that were considered AEs by the Investigator were presented by treatment group in the AE listings.

Physical examination findings at screening, baseline, and end of study were listed. Changes from baseline to end of study were also presented.

Results

Analysis Population	Moxifloxacin	Ferumoxytol	Placebo	Total
Pharmacokinetic	0	57	0	57
Pharmacodynamic	58	57	57	172
Safety	58	58	58	174

Pharmacodynamic Results: The administration of a suprathreshold regimen of ferumoxytol was not associated with QTcI; a slight decrease in QTcI (2 msec) was noted. There was no clinically relevant relationship between change from Baseline in QTcI and the plasma concentration of ferumoxytol. The slope of the relationship was nearly zero and slightly negative, suggesting that there is a lesser change in QTcI with increasing plasma ferumoxytol concentrations. This correlates with the observed lack of any clinically relevant effect of ferumoxytol on cardiac repolarization from the ECG data.

The results of this "Thorough ECG Trial" showed no sign of an effect of a suprathreshold regimen of ferumoxytol on AV conduction, depolarization or cardiac repolarization as measured by the PR, QRS, or QTc interval durations, or adverse events associated with cardiac dysfunction. There was no effect on heart rate. T wave changes in ECG waveform morphology were identified in 5% of ferumoxytol subjects and were deemed to be of no clinical importance.

Safety Results: Continuous ECG monitoring revealed that a suprathreshold regimen of two doses of 510 mg of ferumoxytol within 24 hours did not increase the QT interval or corrected QT interval.

Except for more frequent tachycardic outlier events (7% of subjects for ferumoxytol as compared to 2% and 4% for moxifloxacin and placebo, respectively), there were no outliers in ECG measures noted in the ferumoxytol group. Moxifloxacin showed more outliers (≥ 30 msec increase in QTc from Baseline) compared to ferumoxytol and placebo. No difference in the QTc results was observed between men and women. Five percent of ferumoxytol treated subjects showed T wave changes, a finding which has no known clinical relevance in this setting. No other morphological changes were observed.

Overall, the study treatments were well tolerated by the subjects. Six subjects experienced rash and pruritus following administration of ferumoxytol; however, these events resolved spontaneously or following medical treatment. None of the subjects experienced an adverse event related to changes in blood pressure or heart rate. The most frequently occurring events of increased serum iron, ferritin, transferrin saturation and iron binding capacity were expected pharmacologic effects of treatment with IV iron at baseline.

Pharmacokinetic Results: Plasma ferumoxytol concentrations demonstrated profiles consistent with a capacity limited elimination process. Overall, the pharmacokinetics of ferumoxytol when administered intravenously as a suprathreshold regimen of two 510 mg doses separated by a 24 hour interval are best described using a two compartment, capacity limited elimination model, with $V_{max} = 14.3$ mg/hr and $K_m = 77.49$ mg/L. The addition of weight as a covariate on central volume of distribution significantly improved the pharmacokinetic parameter predictions.

Table: Parameter Estimates and Standard Errors for the Final Two-Compartment PK Model Including Weight Effect on Central Volume of Distribution

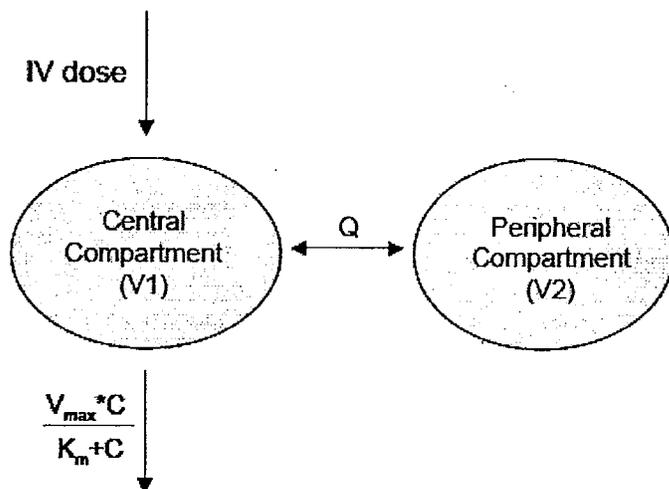
Parameter	Population Mean		Magnitude of Interindividual Variability (%CV)	
	Final Estimate	%SEM	Final Estimate	%SEM
	Central Volume of Distribution (V_1) (L)	2.71	1.8	12.00
Maximum Elimination Rate (V_{max}) (mg/hr)	14.3	1.3	10.00	35.8
Michaelis-Menten Constant (K_m) (mg)	210a	7.5	14.70	59.3
Distribution 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 Relationship Between Weight and V_1 (L/kg)	0.0228	14.8		
Residual Variability (%CV)	7.07	15.9		

Min. value of objective function = 7826.709

^a K_m as a concentration value = 77.49 mg/L

Diagram of Structural two compartment, capacity limited model

Two Compartment



Where:

IV Dose = the dose of ferumoxytol (mg),

V_{max} = the maximum elimination rate from the plasma (mg/hr),

K_m = the plasma concentration (µg Fe/mL) at half maximal rate of elimination from the plasma (estimated as an amount in NONMEM® and converted to a concentration),

C = the plasma ferumoxytol concentration (µg Fe/mL),

Q = the distributional clearance between the central and peripheral compartments for the two-compartment model (L/hr),

V₁ = the volume of distribution of the central compartment, and

V₂ = the volume of distribution of the peripheral compartment.

Since the two administered ferumoxytol doses were separated by only 24 hours, the observed plasma ferumoxytol concentrations reflect supratherapeutic levels that are higher than the expected clinical concentrations for the planned dosing regimen of two 510 mg ferumoxytol doses within 5 ± 3 days. As determined directly from the data, mean C_{max} and t_{max} following the first dose were 206 µg/mL and 0.32 hr, respectively. Mean C_{max} and t_{max} following the second dose were 301 µg/mL and 0.6 hr, respectively. The central volume of distribution was estimated to be 2.71 L, and the maximum elimination rate was 14.3 mg/hr.

Plasma ferumoxytol concentration versus time

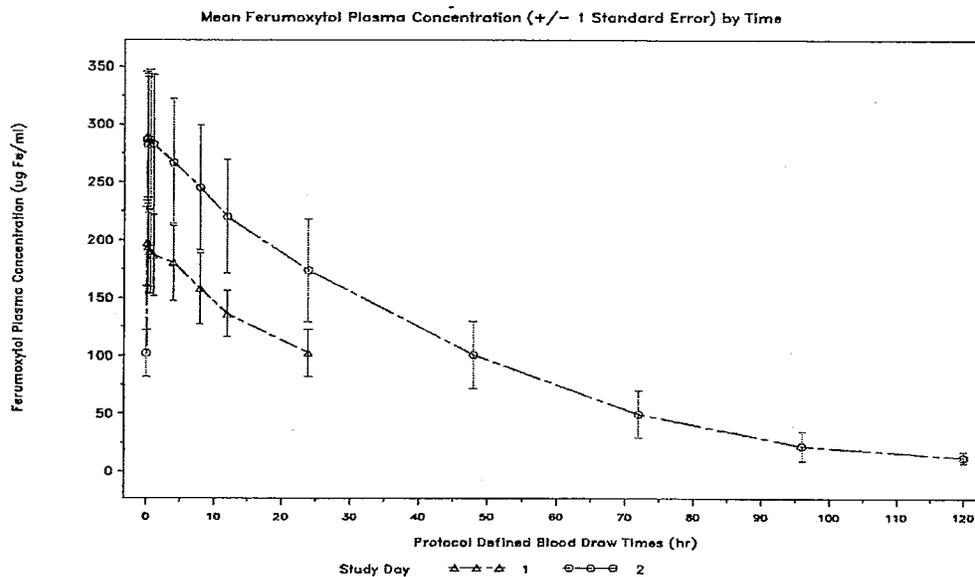
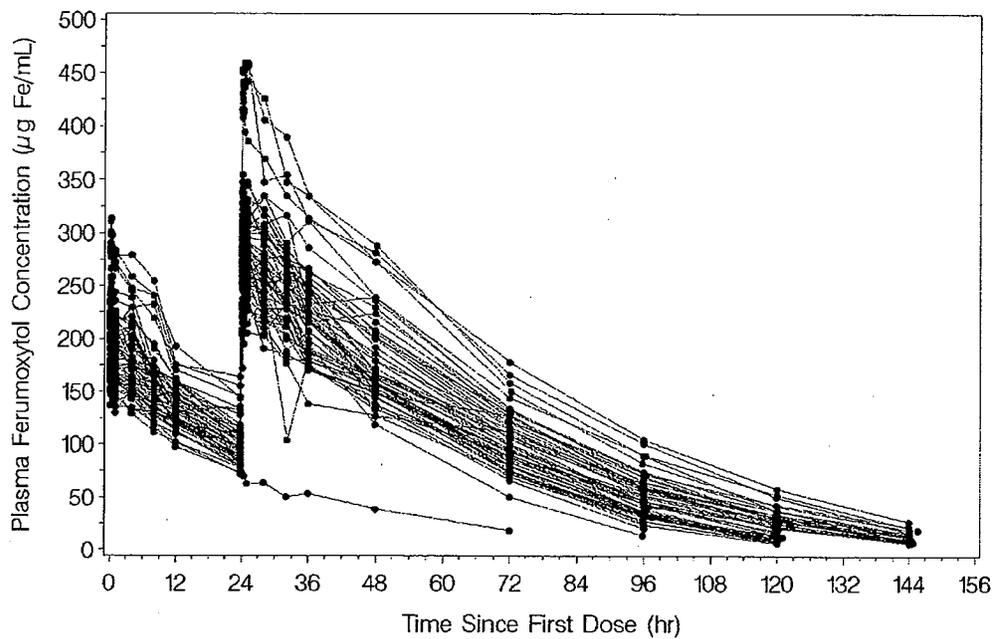


Table.:Pharmacokinetic Parameter Estimates from Noncompartmental Analysis of a Simulated 2 x 510 mg Ferumoxytol Dose Profile^a

Parameter (Units)	Noncompartmental Analysis Results	
λ_z (1/hr)	0.0439	
Terminal $t_{1/2}$ (hr)	15.8	
AUC ₀₋₂₄ ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	3260	
AUC _{last} ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	14700	
AUC _{0-∞} ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	14800	
AUMC _{0-∞} ($\mu\text{g}\cdot\text{hr}^2/\text{mL}$) ^b	697000	
Cl (mL/hr)	69.1	
V _{ss} (mL)	3260	
	Day 1	Day 2
t_{max} (hr) ^c	0.17	24.2
C _{max} ($\mu\text{g}/\text{mL}$)	187	281

^a 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.

^b From the time of the Day 1 dose to time infinity after the Day 2 dose

^c The simulated profile consisted of estimated plasma ferumoxytol concentrations at 10-minute intervals for the first 48 hours, therefore t_{max} would occur at the first data point at 10 minutes after each dose. The t_{max} for the Day 2 dose is therefore 0.2 hrs after the second dose.

Noncompartmental analyses estimated AUC_{0-∞} to be 14,800 $\mu\text{g}\cdot\text{hr}/\text{mL}$, and Day 2 terminal half-life to be 15.8 hr. This model predicted a changing plasma clearance of ferumoxytol over the observed range of concentrations.

CONCLUSION: This study complied with the ICH E14 guidance that all new chemical entities should have a "Thorough ECG Trial." The suprathreshold regimen chosen for this study, 1.02 g ferumoxytol given within 24 hours, was recommended to be the maximal dose of iron that should be given to a healthy volunteer. The positive control was 400 mg moxifloxacin, and the placebo control was intravenous saline. The results showed no effect of a suprathreshold regimen of ferumoxytol on atrio-ventricular conduction, depolarization, or cardiac repolarization as measured by the PR, QRS, QTc interval durations. There was no meaningful effect of ferumoxytol on heart rate. T-wave changes in ECG waveform morphology were identified in 5% of ferumoxytol subjects and were deemed to be of no clinical importance. There was no effect of gender on QTc. Overall, ferumoxytol was well tolerated, as assessed by standard safety assessments.

A two-compartment model with capacity-limited elimination from the central compartment provided the best fit of PK data in this study. This model predicted a changing plasma clearance of ferumoxytol over the observed range of concentrations, which is consistent with previously observed changes in apparent clearance at higher concentrations as observed in a previous Phase I study (7228-01).

62745-3 (Phase 2 study report)

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Title of Study: A Phase II, Open-Label Study of the Safety and Efficacy of Two Parenteral Dose Regimens of Code 7228 (Compared With Oral Iron) as an Iron Replacement Therapy in Chronic Hemodialysis Patients Who Are Receiving Supplemental Erythropoietin (EPO) Therapy (Protocol 62,745-3)

Investigators: Five investigators participated in this study: W. Kline Bolton, MD (Site 301); Mark R. Kaplan, MD (Site 302); Fredric O. Finkelstein, MD (Site 303); Todd W.B. Gehr, MD (Site 304); and Bruce S. Spinowitz, MD (Site 305).

Study Sites: Five sites in the USA participated in this study: Site 301, University of Virginia Health System (Charlottesville, Virginia); Site 302, Nephrology Associates (Nashville, Tennessee); Site 303, Metabolism Associates (New Haven, Connecticut); Site 304, Virginia Commonwealth University (Richmond, Virginia); and Site 305, NY Hospital Medical Center of Queens (Flushing, New York).

Publication (Reference): None.

Study Period: January 2003 through June 2003

Date of Report: 1 July 2005

Phase of Development: 2

Objectives: The study was designed to evaluate the safety and efficacy of 2 parenteral dose regimens of ferumoxytol compared with a control group given oral iron. The primary objective of this clinical study was to assess the impact of ferumoxytol dosing on hemoglobin and iron saturation levels. Secondary objectives of this study were as follows: (1) to assess the impact of ferumoxytol dosing on time to the achievement of the maximum iron saturation and hemoglobin levels; and (2) to evaluate the impact of ferumoxytol dosing on the occurrence of adverse events (AEs), laboratory measurements and deviations, physical examination results, and vital signs.

Methodology: This was an open-label, multicenter study evaluating 2 dose regimens of ferumoxytol (128 mg and 510 mg) and 1 oral iron regimen. Thirty patients were planned for study enrollment: 10 patients (Group 1) were to receive 8 intravenous (IV) doses of 128 mg (4.25 mL) of ferumoxytol, 10 patients (Group 2) were to receive 2 IV doses of 510 mg (17 mL) of ferumoxytol, and 10 patients (Group 3) were to receive 325 mg of oral iron per the manufacturer's instructions. All patients in the lower dose group (128 mg) had their dosing initiated and safety evaluated prior to the enrollment of any higher-dose (510 mg) patients. When the last Group 1 patient received the first of the 8 scheduled doses, the first Group 2 patient was permitted to enter the study. Group 3 patients (oral iron) were eligible for enrollment at any time.

After informed consent had been obtained, screening evaluations were performed 1 to 4 weeks prior to study entry to verify that each patient had satisfied all eligibility criteria. These evaluations included a complete medical history (with current illnesses and symptoms review, as well as documentation of current medications), recording of the weekly EPO doses for the 4 preceding weeks, parathyroid hormone (PTH) collection, and assessments of aluminum and occult blood in stool.

Additional evaluations included the following, performed at screening and at other protocol-defined time points:

- Physical examination: screening and 1 week after completion of dose regimen.
- Vital signs monitoring (pulse rate, blood pressure [BP], temperature, respiration rate [RR])
- For ferumoxytol patients, vital signs were taken at screening, within 45 minutes predose, and weekly through Week 8; pulse and BP were also measured at 15 (\pm 5) minutes, 30 (\pm 5) minutes, and 60 (\pm 5) minutes postdose.
- For oral iron (control) patients, vital signs were taken at screening and weekly for 8 weeks.
- Clinical laboratory evaluations (complete blood count [CBC], iron metabolism panel, serum assays, and clotting function panel)
- For ferumoxytol patients, clinical laboratory evaluations were conducted at screening and within 3 days predose. CBC and iron metabolism were measured weekly for 8 weeks following the initial dose of ferumoxytol; all other postbaseline laboratory evaluations were measured 1 week following the completion of the ferumoxytol dosing regimen.

- For oral iron (control) patients, clinical laboratory evaluations were conducted at screening and when initially enrolled into the control group. CBC and iron metabolism were measured weekly for 8 weeks; all other postbaseline laboratory evaluations were measured at 4 weeks after enrollment.
- Weekly EPO dose was recorded throughout the study for all patients.
- AEs were monitored continuously; assessments were made at each visit, and unsolicited/spontaneous reports were recorded.

Number of Patients: A total of 36 patients (21 males, 15 females) were enrolled in the study: 15 patients were enrolled in Group 1 (8 x 128 mg ferumoxytol), 11 patients were enrolled in Group 2 (2 x 510 mg ferumoxytol, and 10 patients were enrolled in Group 3 (oral iron).

Diagnosis and Main Criteria for Inclusion: Male or female patients at least 18 years of age who were undergoing chronic hemodialysis and had received stable supplemental EPO therapy ($\pm 25\%$ of selected dose) for ≥ 4 weeks, whose hemoglobin was ≤ 12 g/dL, and whose transferrin saturation (TSAT) was $\leq 30\%$.

Test Product, Dose, Mode of Administration, and Lot Number:

Group 1: 8 IV bolus doses of 128 mg (4.25 mL) ferumoxytol within 30 minutes after starting dialysis session.

Group 2: 2 IV bolus doses of 510 mg (17 mL) ferumoxytol within 30 minutes after starting dialysis session. The lots of ferumoxytol used for this study were 01051501 and 01062601.

Duration of Treatment: Patients in the low and high dose groups, respectively, received 8 and 2 bolus doses of ferumoxytol. The total duration of any patient's participation in the study (including screening [1 to 4 weeks prior to the first dose] and follow-up [8 weeks after regimen initiation]) was up to 12 weeks for patients in each group.

Reference Therapy, Dose, Mode of Administration, and Batch Number(s):

Oral iron: 325 mg daily oral iron maintained for a minimum of 8 sequential dialysis sessions
Oral iron was administered per the manufacturer's instructions.

Criteria for Evaluation:

Efficacy: The primary efficacy endpoints were the mean changes from baseline in hemoglobin and TSAT for 8 weeks following the initial dose of study drug; these endpoints were selected to evaluate ferumoxytol's ability to elevate hemoglobin and TSAT above baseline values. Additionally, the change from baseline was evaluated for hematocrit, serum iron, serum ferritin, and reticulocytes. The times to maximum response (level) for hemoglobin, hematocrit, TSAT, and serum ferritin were secondary endpoints in this study.

Safety: Safety assessments included AE monitoring and changes in clinical laboratory evaluations, physical examination, and vital signs.

Statistical Methods: Efficacy parameters (hemoglobin, hematocrit, TSAT, and serum ferritin) were summarized descriptively (N, mean, SD, median, minimum, and maximum) at each time point, and change from baseline was summarized at each follow-up time point by treatment group. A repeated measures linear model was fit in order to determine the average effect of treatment and measurement time for each measured efficacy parameter. The model included the fixed main effects of treatment and time, and the interaction between treatment and time, on the change in each parameter. Testing of both main effects was 2-sided, with significance declared at $\alpha = 0.05$; the interaction between treatment and time was declared significant at $\alpha = 0.10$ (2-sided testing). Time to maximum level for hemoglobin, hematocrit, TSAT, and serum ferritin was summarized descriptively for each parameter by treatment group.

All reported AEs were mapped to system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities Terminology (MedDRA) dictionary. Treatment-emergent AEs were summarized (n, %) by an overall summary and by dose group for all AEs and treatment related AEs. Treatment-emergent AEs were also summarized by maximum intensity.

All data listings, summaries, and statistical analyses were generated using SAS Version 8 or higher.

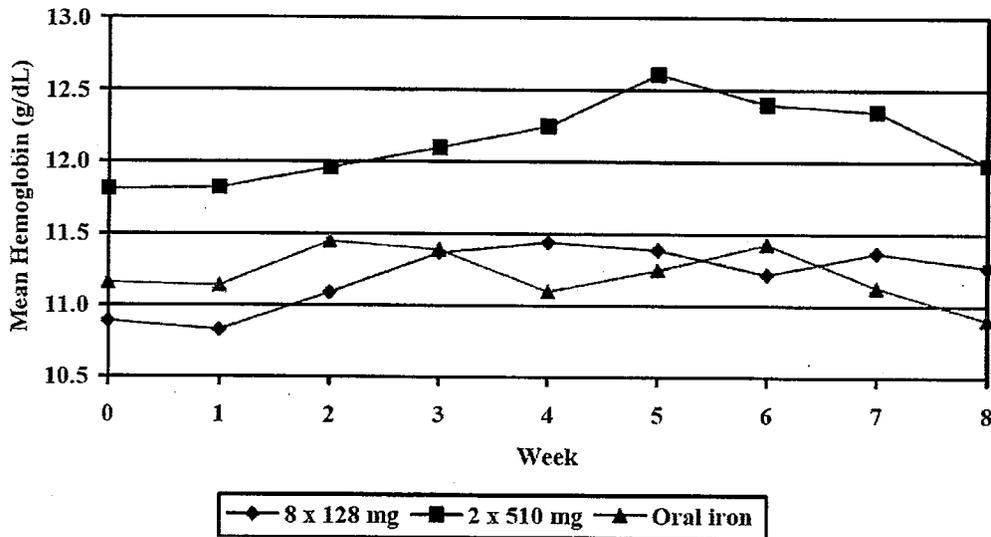
RESULTS

Efficacy Results: Results for the primary efficacy parameter were as expected for a metabolized iron oxide drug. Hemoglobin values rose gradually following dosing with ferumoxytol. Mean hemoglobin for patients who received 8 x 128 mg ferumoxytol rose from 10.89 ± 0.80 g/dL at baseline to a maximum of 11.44 ± 1.21 g/dL at

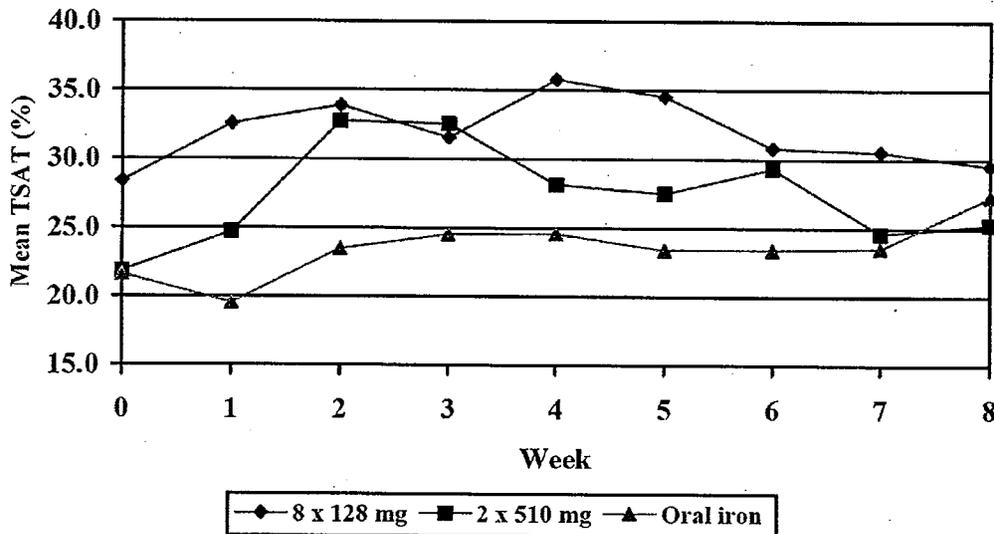
Week 4. For patients who received 2 x 510 mg ferumoxytol, mean hemoglobin levels rose from 11.81 ± 1.01 g/dL at baseline to a maximum of 12.61 ± 1.03 g/dL at Week 5. For patients who received daily oral iron, mean hemoglobin levels rose from 11.16 ± 0.54 g/dL at baseline to a maximum of 11.45 ± 0.69 g/dL at Week 2. TSAT values rose quickly in patients who received ferumoxytol. For patients who received 8 ± 128 mg ferumoxytol, TSAT rose from 28.38% ± 16.97% at baseline to a peak of 35.76% ± 18.01% at Week 4. For patients who received 2 ± 510 mg ferumoxytol, TSAT rose from 21.85% ± 10.41% at baseline to a peak of 32.76% ± 11.59% at Week 2. In contrast, TSAT rose gradually in patients who received oral iron, from 21.61% ± 5.63% at baseline to a peak of 27.28% ± 9.91% at Week 8.

Parameter	Week	Ferumoxytol								
		8 × 128 mg			2 × 510 mg			Oral Iron		
		N	Mean	SD	N	Mean	SD	N	Mean	SD
Hemoglobin (g/dL)	0	10	10.89	0.80	11	11.81	1.01	10	11.16	0.54
	1	10	10.83	0.90	11	11.82	0.88	10	11.14	0.75
	2	10	11.09	0.91	11	11.96	1.34	10	11.45	0.69
	3	10	11.37	1.22	11	12.10	1.37	10	11.39	0.96
	4	10	11.44	1.21	11	12.25	1.13	9	11.10	1.24
	5	10	11.39	1.17	10	12.61	1.03	8	11.25	0.88
	6	10	11.22	1.34	11	12.40	0.96	7	11.43	1.11
	7	10	11.37	1.41	11	12.35	0.69	6	11.13	0.97
	8	10	11.27	1.48	10	11.98	0.95	5	10.90	0.31
TSAT (%)	0	9	28.38	16.97	11	21.85	10.41	9	21.61	5.63
	1	10	32.56	15.62	10	24.70	11.89	9	19.53	5.84
	2	10	33.88	16.82	11	32.76	11.59	10	23.48	6.59
	3	10	31.55	16.51	11	32.54	19.00	9	24.51	14.11
	4	10	35.76	18.01	11	28.14	20.88	9	24.56	7.88
	5	9	34.54	16.75	10	27.50	5.85	8	23.41	8.18
	6	9	30.81	14.20	11	29.35	11.49	7	23.43	4.83
	7	10	30.53	17.87	11	24.60	11.39	6	23.52	5.13
	8	10	29.54	16.41	11	25.25	10.39	6	27.28	9.91

Hemoglobin values over time



Transferrin saturation over time



Reticulocytes increased after dosing for both dose groups of ferumoxytol, indicating that the iron was being utilized for erythropoiesis. Reticulocytes peaked at Week 4 for patients who received 8 x 128 mg ferumoxytol and at Week 2 for patients who received 2 x 510 mg ferumoxytol. For patients who received daily oral iron, reticulocytes decreased from baseline at Week 1, then rebounded and were increased from baseline for the remainder of the study, reaching a peak at Week 8. As expected, serum iron increased in parallel to TSAT. Serum ferritin peaked at Week 2 for patients who received 2 x 510 mg ferumoxytol and at Week 3 for patients who received 8 x 128 mg ferumoxytol. Serum ferritin gradually decreased with time, as would be expected for a measurement that reflects stored iron. Both doses of ferumoxytol indicated significant differences in the changes

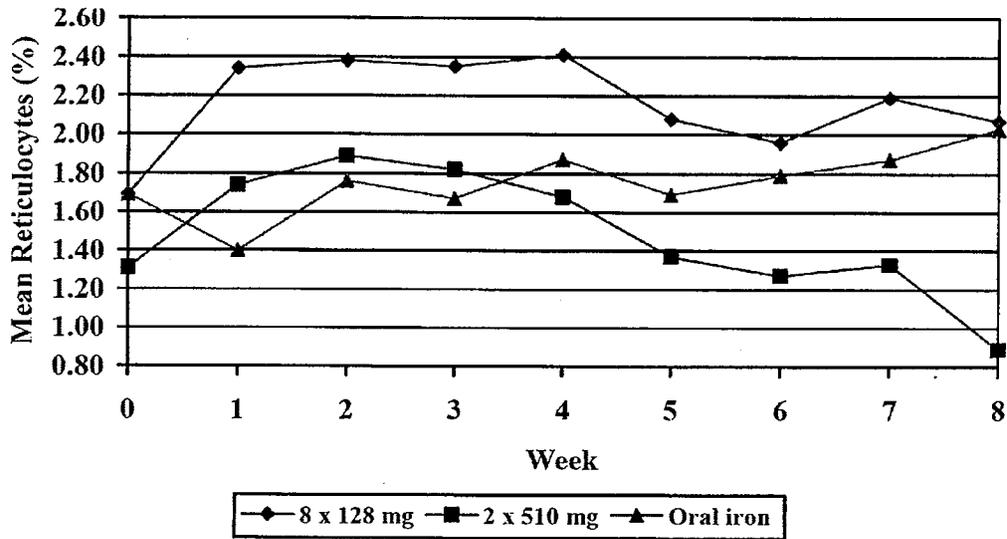
from baseline in serum ferritin when compared individually with oral iron ($p < 0.0001$). Hematocrit values paralleled those observed for hemoglobin, with similar statistical results.

Secondary iron metabolism measures (efficacy evaluable population)

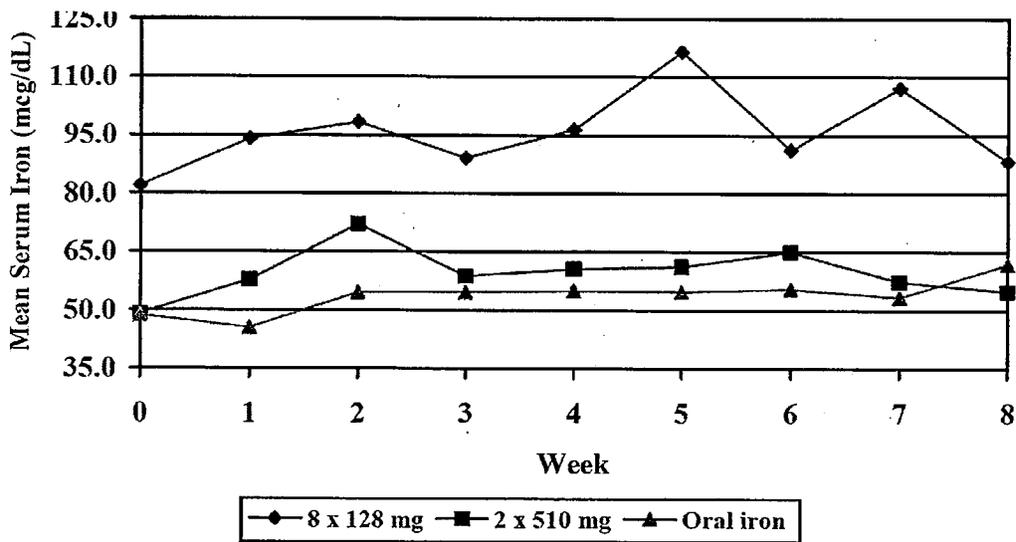
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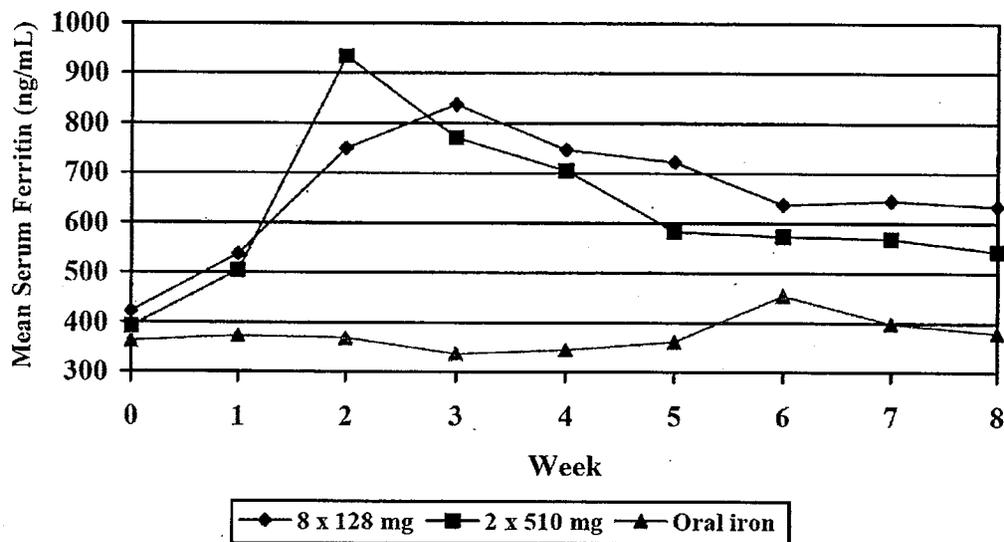
Parameter	Week	Ferumoxytol						Oral Iron		
		8 × 128 mg			2 × 510 mg			N	Mean	SD
		N	Mean	SD	N	Mean	SD			
Reticulocytes (%)	0	7	1.69	1.00	9	1.31	0.56	9	1.69	0.62
	1	9	2.34	0.88	11	1.74	0.76	9	1.40	0.66
	2	9	2.38	1.06	11	1.89	0.95	10	1.76	0.59
	3	10	2.35	0.87	11	1.82	1.08	10	1.67	0.68
	4	10	2.41	1.07	11	1.68	0.77	9	1.87	0.67
	5	10	2.08	0.80	10	1.37	0.88	8	1.69	0.74
	6	9	1.96	0.93	11	1.27	0.79	7	1.79	0.86
	7	10	2.19	1.03	10	1.33	0.72	6	1.87	0.97
	8	10	2.07	1.48	10	0.89	0.34	6	2.03	0.97
Serum Iron (µg/dL)	0	9	81.89	82.42	11	49.09	17.56	9	48.67	17.44
	1	10	94.00	76.69	10	57.70	24.28	9	45.44	17.72
	2	10	98.30	85.86	11	72.09	27.33	10	54.60	15.48
	3	10	89.10	79.43	11	58.73	12.24	9	54.67	31.97
	4	10	96.40	84.10	11	60.55	44.18	9	55.00	20.39
	5	9	116.44	117.34	11	61.18	10.90	8	54.75	20.91
	6	9	91.11	85.66	11	65.00	21.61	7	55.43	15.99
	7	10	107.10	121.26	11	57.36	19.98	6	53.33	15.76
	8	10	88.20	86.04	11	54.82	18.69	6	61.83	28.91
Serum Ferritin (ng/mL)	0	9	422.36	220.57	11	391.39	288.93	9	362.56	240.70
	1	10	537.77	271.01	10	504.40	268.59	9	373.00	240.70
	2	10	749.62	314.21	11	933.82	457.62	10	368.50	251.16
	3	10	837.50	376.43	11	770.85	400.35	10	337.00	220.17
	4	10	746.46	347.88	11	704.68	464.61	9	344.89	259.69
	5	9	721.86	359.58	11	582.23	351.66	8	361.13	248.38
	6	9	636.91	302.75	11	573.55	346.33	7	454.00	414.93
	7	10	644.69	339.12	11	568.19	363.59	6	398.50	156.19
	8	10	633.95	333.31	11	543.11	347.38	6	379.17	172.58
Hematocrit (%)	0	10	32.61	2.71	11	35.77	2.48	10	34.03	1.86
	1	10	32.92	3.16	11	35.83	2.42	10	33.93	2.34
	2	10	33.39	2.95	11	36.44	3.80	10	35.04	2.05
	3	10	34.04	3.70	11	36.83	3.96	10	34.67	3.06
	4	10	34.70	3.98	11	37.27	2.89	9	33.76	3.89
	5	10	34.17	3.31	10	38.74	3.46	8	34.49	3.36
	6	10	33.86	4.10	11	38.07	2.55	7	35.41	3.29
	7	10	34.30	4.34	11	37.72	2.26	6	34.68	2.84
	8	10	33.93	4.43	10	36.49	3.09	5	33.46	0.92

Reticulocytes over time



Serum iron over time





For ferumoxytol-treated patients overall, mean EPO doses for the efficacy evaluable population were reduced from baseline values for Weeks 3 through 8, indicating improvement in erythropoiesis. However, much of this combined-treatment data was driven by patients who received 2 x 510 mg ferumoxytol.

Table: Time to Maximum Level of Iron Metabolism Parameters, Hemoglobin, and Hematocrit

Parameter Descriptive Statistics	Ferumoxytol		
	8 x 128 mg N = 10	2 x 510 mg N = 11	Oral Iron N = 10
Time (days) to maximum level of TSAT			
Mean ± SD	26.70 ± 15.30	19.73 ± 15.20	33.50 ± 15.18
Time (days) to maximum level of serum ferritin			
Mean ± SD	23.50 ± 8.09	14.73 ± 8.38	32.20 ± 19.34
Time (days) to maximum level of hemoglobin			
Mean ± SD	34.40 ± 15.52	33.45 ± 12.96	37.10 ± 17.90
Time (days) to maximum level of hematocrit			
Mean ± SD	32.10 ± 17.90	37.09 ± 10.90	36.60 ± 18.19

On average, maximum levels of TSAT, serum ferritin, hemoglobin, and hematocrit were reached sooner in patients who received ferumoxytol than in patients who received daily oral iron. Of the 2 ferumoxytol dose groups, maximum levels of TSAT, serum ferritin, and hemoglobin were reached sooner in patients who received 2 x 510 mg ferumoxytol than in patients who received 8 x 128 mg ferumoxytol. Hemoglobin and hematocrit production followed the establishment of saturated iron stores.

Safety Results: Eighteen (69.2%) patients who received ferumoxytol and 4 (40.0%) patients who received oral iron had 1 or more treatment-emergent AEs, regardless of relationship to study drug. Five (19.2%) patients who received ferumoxytol and 2 (20.0%) patients who received oral iron had a treatment-emergent AE that was considered by the investigator to be related to study drug. Four (15.4%) patients who received ferumoxytol were withdrawn from the study because of treatment-related AEs; no patient who received oral iron was withdrawn from the study due to an AE.

No patient died during the study. Two patients (1 who received 8 x 128 mg ferumoxytol and 1 who received 2 x 510 mg ferumoxytol) had nonfatal SAEs (diarrhea, atrial fibrillation, congestive heart failure). None of these events was considered by the investigator to be related to drug administration.

In the clinical laboratory evaluation, analyses were comparable between dose groups in both the change from baseline and shifts over time. There were no discernable differences between treatments in outcomes of electrolyte and hepatic function or in clotting function. Among vital signs parameters, no obvious influence of ferumoxytol on the direction or magnitude of changes in RR or temperature was observed in either dose group; however, slight decreases in mean BP and mean pulse rate were observed at most time points.

Conclusions:

- Both dose regimens of ferumoxytol increased hemoglobin, hematocrit, and reticulocyte levels, which indicate that the iron was able to stimulate erythropoiesis.
- Both dose regimens of ferumoxytol transiently increased TSAT and serum iron levels, which indicates normal iron transport.
- Both dose regimens of ferumoxytol increased ferritin levels, which indicates the iron that was not immediately needed for erythropoiesis was transported to storage sites.
- On average, maximum levels of TSAT, serum ferritin, hemoglobin, and hematocrit were reached sooner in patients who received ferumoxytol than in patients who received daily oral iron.

Of the 2 ferumoxytol dose groups, maximum levels of TSAT, serum ferritin, and hemoglobin were reached sooner in patients who received 2 x 510 mg ferumoxytol than in patients who received 8 x 128 mg ferumoxytol.

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62745-4 (phase II study)

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Title of Study: A Phase II, Open-Label Study of the Safety and Efficacy of Two Parenteral Dose Regimens of Code 7228 (ferumoxytol) as an Iron Replacement Therapy in Patients With Chronic Kidney Disease or Patients on Peritoneal Dialysis (Protocol 62,745-4)

Investigators: Three investigators participated in this study: W. Kline Bolton, MD (Site 401); Mark R. Kaplan, MD (Site 402); and Bruce S. Spinowitz, MD (Site 404).

Study Sites: Three sites in the USA participated in this study: Site 401, University of Virginia (Charlottesville, Virginia); Site 402, Nephrology Associates (Nashville, Tennessee); and Site 404, NY Hospital Medical Center of Queens (Flushing, New York).

Publication (Reference): Spinowitz BS, Schwenk MH, Jacobs PM, et al. *The safety and efficacy of ferumoxytol therapy in anemic chronic kidney disease patients* [not yet accepted for publication]; 2005.

Study Period: October 2002 through December 2002

Date of Report: 18 February 2005

Phase of Development: 2

Objectives: This study was designed to evaluate the safety and efficacy of 2 parenteral dose regimens of Code 7228 (ferumoxytol) in patients with chronic renal failure (specifically, patients who were not on dialysis), or who were on peritoneal dialysis. The primary objective was to assess the impact of ferumoxytol dosing on hemoglobin and iron saturation levels. Secondary objectives were as follows: (1) to assess the impact of ferumoxytol dosing on time to achievement of the maximum iron saturation and hemoglobin levels; and (2) to evaluate the impact of ferumoxytol dosing on the occurrence of adverse events (AEs), laboratory measurements and deviations, physical examination results, and vital signs.

Methodology: This was an open-label, multicenter study evaluating 2 dose regimens of ferumoxytol. Twenty patients were planned for study enrollment: 10 patients (Group 1) were to receive 4 intravenous (IV) doses of 255 mg (8.5 mL) of ferumoxytol (with 2 to 3 days between doses), and 10 patients (Group 2) were to receive 2 IV doses of 510 mg (17 mL) of ferumoxytol (with 2 to 7 days between doses). All patients in Group 1 (4 × 255 mg) had their dosing initiated and safety evaluated prior to the enrollment of any Group 2 (2 × 510 mg) patients. When the last Group 1 patient received the first of the 4 scheduled doses, the first Group 2 patient was permitted to enter the study.

Dosing Regimens

Group	N	Dose	Frequency
Group 1	10	4 doses of 255 mg (8.5 mL) ferumoxytol	Once every 2 to 3 days
Group 2	10	2 doses of 510 mg (17 mL) ferumoxytol	Once every 2 to 3 days, or weekly

After informed consent had been obtained, screening evaluations were performed 1 to 4 weeks prior to study entry to verify that each patient had satisfied all eligibility criteria. These evaluations included a complete medical history (with current illnesses and symptoms review, as well as documentation of current medications), parathyroid hormone (PTH) collection, and assessments of aluminum and occult blood in stool.

Additional evaluations included the following, performed at screening and at other protocol-defined time points:

- Physical examination: screening and 1 week after completion of dose regimen.
- Vital signs monitoring (pulse rate, blood pressure [BP], temperature, respiration rate [RR]): screening, within 45 minutes predose, and at 15 (±5) minutes, 30 (±5) minutes, and 60 (±15) minutes postdose. After the last dose, vital signs were collected weekly through the end of the study (Weeks 3–8 for Group 1, Weeks 2–8 for Group 2).

- Clinical laboratory evaluations (complete blood count [CBC], iron metabolism panel, serum assays, and clotting function panel): screening and within 3 days predose. CBC and iron metabolism were measured weekly for 8 weeks following the initial dose of ferumoxytol; all other postbaseline laboratory evaluations were only measured 1 week following the completion of the ferumoxytol dosing regimen.
- AEs were monitored continuously; assessments were made at each visit and unsolicited/spontaneous reports were recorded.

Number of Patients: A total of 21 patients (9 males, 12 females) were enrolled in the study: 10 patients received 4 IV doses of 255 mg ferumoxytol, and 11 patients received 2 IV doses of 510 mg ferumoxytol.

Diagnosis and Main Criteria for Inclusion: Male or female patients at least 18 years of age, who were not on hemodialysis and had chronic kidney failure or who were undergoing peritoneal dialysis, whose hemoglobin was ≤ 12 g/dL, and whose transferrin saturation (TSAT) was $\leq 30\%$.

Test Product, Dose, Mode of Administration, and Lot Number:

Group 1: 4 IV bolus doses of 255 mg (8.5 mL) ferumoxytol (with 2 to 3 days between doses)

Group 2: 2 IV bolus doses of 510 mg (17 mL) ferumoxytol (with 2 to 7 days between doses)

A single lot of ferumoxytol was used for this study: Lot 01051501.

Duration of Treatment: Patients in the low and high dose groups, respectively, received 4 and 2 bolus doses of ferumoxytol. The total duration of any patient's participation in the study (including screening [1 to 4 weeks prior to the first dose] and follow-up [8 weeks after regimen initiation]) was up to 12 weeks for patients in each group.

Reference Therapy, Dose, Mode of Administration, and Batch Number(s): None.

Criteria for Evaluation:

Efficacy: The primary efficacy endpoints were the mean changes from baseline in hemoglobin and TSAT for 8 weeks following the initial dose of ferumoxytol; these endpoints were selected to evaluate ferumoxytol's ability to elevate hemoglobin and TSAT over baseline. The secondary efficacy endpoints included elevation of reticulocytes, serum iron, serum ferritin, and hematocrit over baseline. The times to maximum response (level) for hemoglobin, hematocrit, TSAT, and serum ferritin were secondary endpoints in this study.

Safety: Safety assessments included AE monitoring and changes in clinical laboratory evaluations, physical examination, and vital signs.

Statistical Methods: Efficacy parameters (hemoglobin, hematocrit, TSAT, and serum ferritin) were summarized descriptively (N, mean, SD, median, minimum, and maximum) at each time point, and change from baseline was summarized at each follow-up time point, by ferumoxytol dose group and overall. A repeated measures linear model was fit in order to determine the average effect of ferumoxytol dose and measurement time, and the interaction between treatment and time, on the change in each parameter. Testing of both main effects was 2-sided, with significance declared at $\alpha=0.05$; the interaction between treatment and time was declared significant at $\alpha=0.10$ (2-sided testing). In the event that the time effect was statistically significant at the $\alpha=0.05$ level, multiple comparisons were made between mean parameter levels at baseline versus each post baseline time point (i.e., the significance of within-group change was examined), and between changes at postbaseline time points, using a Bonferroni-corrected statistic. Time to maximum level for hemoglobin, hematocrit, TSAT, and serum ferritin was summarized descriptively for each parameter by ferumoxytol dose group.

All reported AEs were mapped to system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities Terminology (MedDRA) dictionary. Treatment-emergent AEs were summarized (n, %) by an overall summary and by dose group for all AEs and treatment-related AEs. Treatment-emergent AEs were also summarized by maximum intensity.

All data listings, summaries, and statistical analyses were generated using SAS Version 8 or higher.

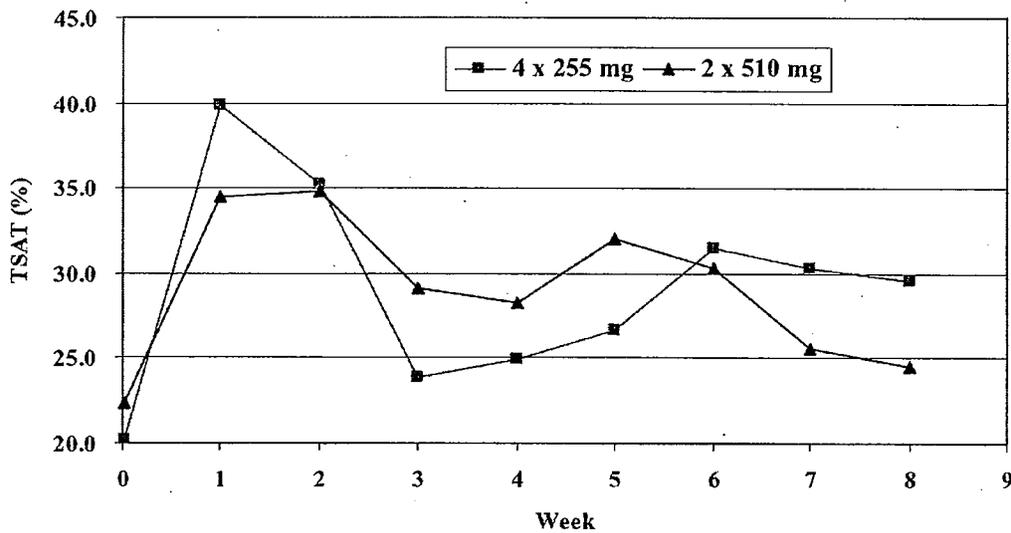
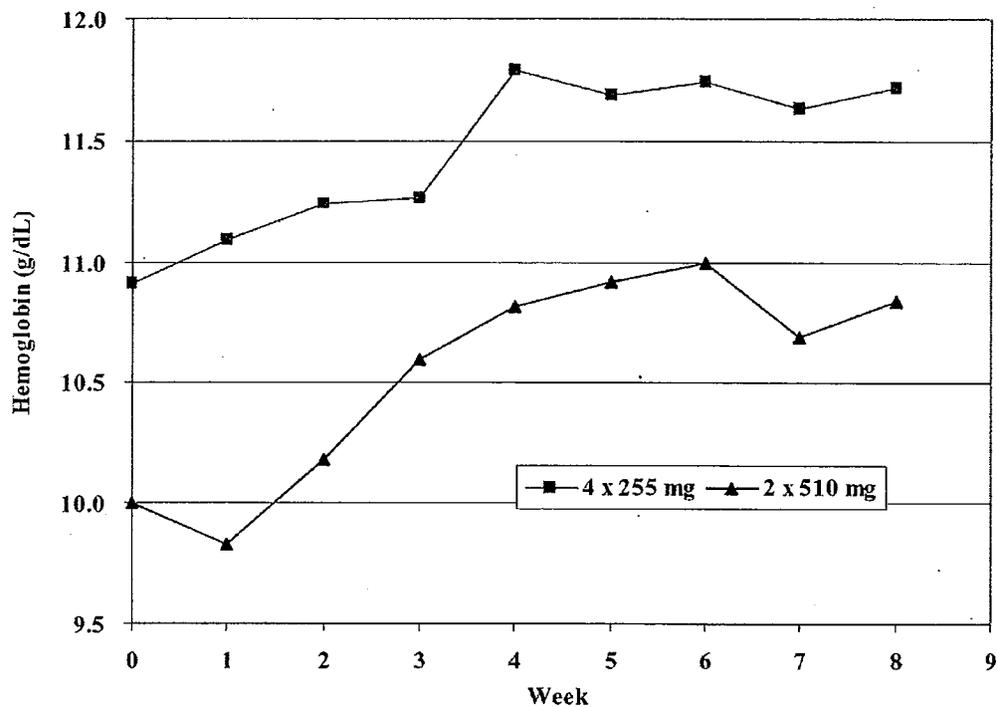
RESULTS

Efficacy Results: Results for the primary efficacy parameter were as expected for a metabolized iron oxide drug. Hemoglobin values rose gradually following dosing with ferumoxytol, with a broad peak at 4 to 6 weeks after the first dose; Group 1 showed a maximum mean increase of 0.88 g/dL at Week 4, and Group 2 showed a

maximum mean increase of 1.00 g/dL at Week 6. Overall, the change in hemoglobin varied over time ($p < 0.0001$). Mean TSAT values rose quickly, from 20.2% \pm 3% at baseline to a peak of 39.9% \pm 7.9% at Week 1 in patients who received 4 x 255 mg ferumoxytol, and from 22.4% \pm 12.3% at baseline to a peak of 34.8% \pm 14.3% at Week 2 for patients who received 2 x 510 mg ferumoxytol. On average, the change in TSAT varied over time ($p < 0.0001$).

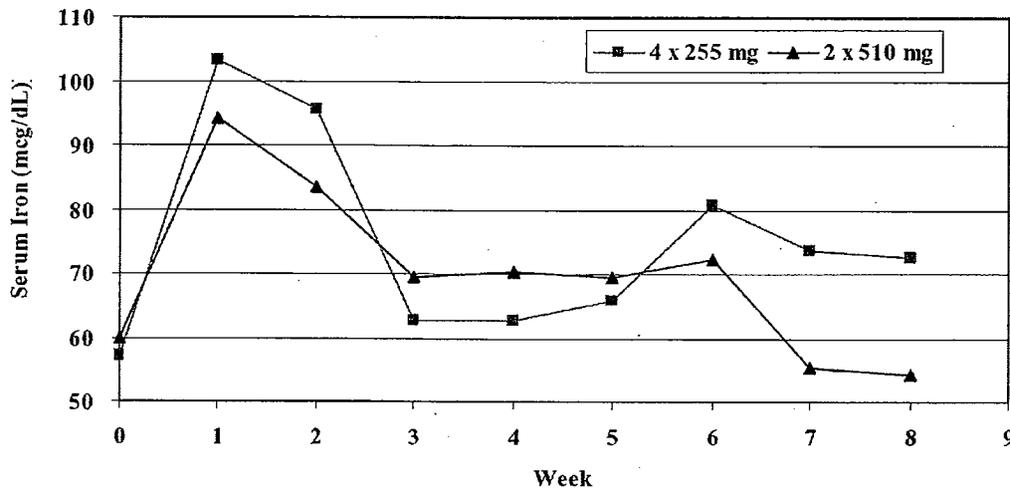
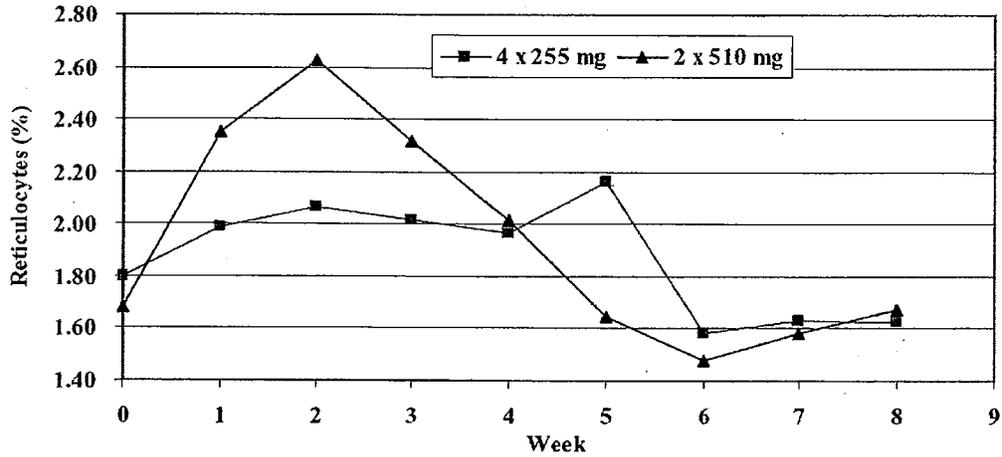
Parameter	Week	Ferumoxytol								
		4 x 255 mg Iron ^a			2 x 510 mg Iron ^a			Total		
		N	Mean	SD	N	Mean	SD	N	Mean	SD
Hemoglobin (g/dL)	0	10	10.91	1.26	11	10.00	1.25	21	10.43	1.31
	1	10	11.09	0.81	11	9.83	1.10	21	10.43	1.15
	2	10	11.24	1.09	11	10.18	1.15	21	10.69	1.22
	3	10	11.26	0.90	11	10.60	1.06	21	10.91	1.02
	4	10	11.79	0.75	11	10.82	1.29	21	11.28	1.15
	5	10	11.69	0.91	9	10.92	1.19	19	11.33	1.10
	6	10	11.74	0.85	10	11.00	1.37	20	11.37	1.17
	7	10	11.63	0.83	10	10.69	1.40	20	11.16	1.22
	8	10	11.72	0.81	10	10.84	1.43	20	11.28	1.22
TSAT (%)	0	10	20.20	7.33	11	22.36	12.25	21	21.33	10.02
	1	10	39.90 ^b	7.94	11	34.45	30.09	21	37.05	22.11
	2	10	35.20 ^b	16.51	11	34.82	14.25	21	35.00	14.97
	3	10	23.90	7.52	11	29.09	11.01	21	26.62	9.65
	4	10	24.90	7.40	11	28.27	14.13	21	26.67	11.29
	5	10	26.70	5.52	8	32.00	7.23	18	29.06	6.71
	6	10	31.47 ^b	6.60	10	30.30	12.27	20	30.89	9.61
	7	10	30.30 ^b	8.72	9	25.56	13.47	19	28.05	11.16
	8	10	29.60 ^b	8.03	10	24.50	8.95	20	27.05	8.68

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Reticulocytes increased after dosing for both dose groups of ferumoxytol, indicating that the iron was being utilized for erythropoiesis. This increase was more pronounced in Group 2, whose population was more anemic at baseline. Serum iron increased in parallel to TSAT, as expected, peaking at Week 1 for both dose groups of ferumoxytol. Serum ferritin levels rose sharply after dosing for both groups of ferumoxytol, and then gradually decreased over time, providing evidence that the drug was being metabolized and added to iron stores. Hematocrit values paralleled those observed for hemoglobin, with similar statistical results. There was a reduction noted in mean EPO doses from baseline at all time points during the study, especially for Group 2, indicating improvement in erythropoiesis.

On average, maximum TSAT and serum ferritin values were reached in 16 to 19 days among patients in the overall ferumoxytol group. Hemoglobin and hematocrit production followed the establishment of saturated iron stores, with the mean times to maximum level of 41 days in patients who received 4 x 255 mg ferumoxytol, and 35 days in patients who received 2 x 510 mg ferumoxytol.



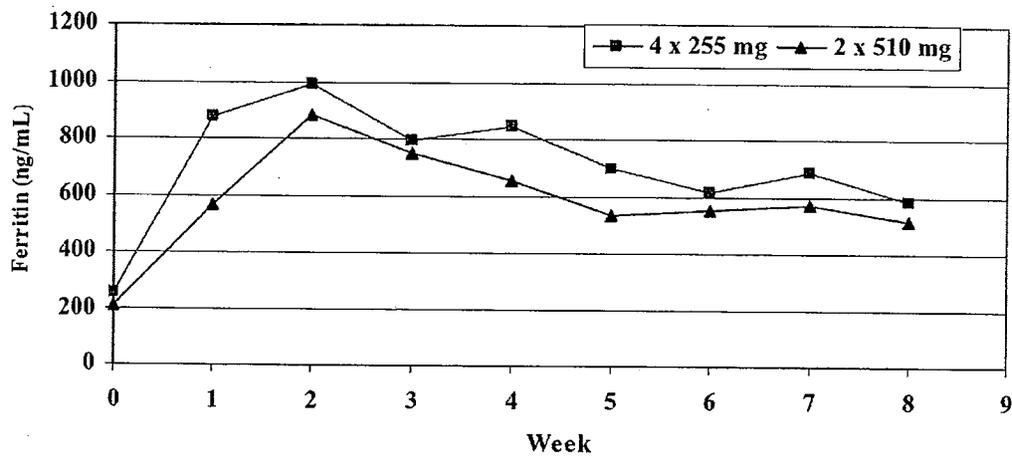


Table: Time to Maximum Level of Iron Metabolism Parameters, Hemoglobin, and Hematocrit

Parameter Descriptive Statistics	Ferumoxylol		
	4 x 255 mg Iron N = 10	2 x 510 mg Iron N = 11	Total N = 21
Time (days) to maximum level of TSAT			
Mean ± SD	15.10 ± 13.20	16.64 ± 12.26	15.90 ± 12.42
Time (days) to maximum level of serum ferritin			
Mean ± SD	20.80 ± 12.29	16.55 ± 10.82	18.57 ± 11.46
Time (days) to maximum level of hemoglobin			
Mean ± SD	41.50 ± 13.52	35.00 ± 13.24	38.10 ± 13.45
Time (days) to maximum level of hematocrit			
Mean ± SD	41.00 ± 12.78	35.00 ± 13.24	37.86 ± 13.06

Parameter	Week	Ferumoxytol								
		4 × 255 mg Iron ^a			2 × 510 mg Iron ^a			Total		
		N	Mean	SD	N	Mean	SD	N	Mean	SD
Reticulocytes (%)	0	9	1.80	0.64	11	1.68	0.95	20	1.74	0.81
	1	7	1.99	0.90	11	2.35	0.83	18	2.21	0.85
	2	10	2.06	1.04	11	2.63	1.41	21	2.36	1.25
	3	10	2.02	0.76	10	2.32	0.74	20	2.17	0.74
	4	10	1.97	0.71	11	2.02	0.75	21	1.99	0.71
	5	9	2.16	0.61	9	1.64	0.73	18	1.90	0.71
	6	10	1.58	0.87	10	1.48	0.82	20	1.53	0.83
	7	10	1.63	0.90	9	1.58	0.76	19	1.61	0.82
	8	10	1.63	0.92	10	1.68	0.77	20	1.65	0.83
Serum Iron (µg/dL)	0	10	57.10	18.23	11	59.91	33.71	21	58.57	26.83
	1	10	103.30	20.46	11	94.27	92.58	21	98.57	67.05
	2	10	95.50	59.92	11	83.55	35.95	21	89.24	47.95
	3	10	62.60	19.20	11	69.36	29.45	21	66.14	24.73
	4	10	62.70	18.39	11	70.36	48.00	21	66.71	36.32
	5	10	65.80	13.16	9	69.33	29.92	19	67.47	22.09
	6	10	80.70	19.61	10	72.30	35.53	20	76.50	28.26
	7	10	73.70	24.04	10	55.30	40.88	20	64.50	33.98
	8	10	72.60	25.48	10	54.10	28.05	20	63.35	27.75
Serum Ferritin (ng/mL)	0	10	251.50	258.93	10	211.50	176.66	20	231.50	216.71
	1	9	874.00	380.93	10	563.41	437.64	19	710.53	430.86
	2	9	988.11	352.77	11	884.75	378.24	20	931.27	361.22
	3	10	790.90	401.61	11	748.44	374.95	21	768.66	378.61
	4	10	844.40	597.25	10	651.43	374.72	20	747.92	495.26
	5	10	697.28	388.27	9	534.72	335.43	19	620.28	363.78
	6	10	614.34	315.44	10	552.92	319.80	20	583.63	310.76
	7	10	684.63	315.37	10	573.69	396.00	20	629.16	353.03
	8	10	583.56	290.17	10	512.07	304.50	20	547.82	291.80
Hematocrit (%)	0	10	33.89	3.30	11	30.30	3.41	21	32.01	3.75
	1	10	33.90	2.74	11	29.69	3.03	21	31.70	3.55
	2	10	34.37	3.50	11	30.71	3.56	21	32.45	3.92
	3	10	34.71	2.90	11	31.90	3.13	21	33.24	3.28
	4	10	36.08	2.58	11	32.73	4.09	21	34.32	3.78
	5	10	35.99	2.63	9	33.50	3.80	19	34.81	3.39
	6	10	36.27	2.19	10	33.25	4.21	20	34.76	3.62
	7	10	35.82	2.47	10	32.32	4.19	20	34.07	3.80
	8	10	35.88	2.50	10	32.77	4.13	20	34.33	3.69

Safety Results: Of the 21 patients enrolled in the study across both dosing groups, a total of 17 patients (81%) had at least 1 treatment-emergent AE; 42.9% of patients had treatment-emergent AEs that were considered to be related to treatment. Within each dose group, 70% of the patients who received 4 x 255 mg ferumoxytol and 91% of the patients who received 2 x 510 mg ferumoxytol had at least 1 treatment-emergent AE. Two (20%) patients who received 4 x 255 mg ferumoxytol had treatment-emergent AEs that were considered to be related to treatment, compared with 7 (63.6%) patients who received 2 x 510 mg ferumoxytol. No patient in either dose group withdrew from the study due to an AE.

During the course of the study, 1 patient died and 4 patients had nonfatal SAEs. No SAE was considered to be related to treatment. SAEs consisted of worsening aortic stenosis (death), acute renal failure, pneumonia,

worsening weakness (asthenia), and complete atrioventricular block. All events except for atrioventricular block were considered to have been preexisting.

In the clinical laboratory evaluation, analyses were comparable between dose groups in both the change from baseline and shifts over time. There were no discernable differences between treatments in outcomes of electrolyte and hepatic function or in clotting function. Among vital signs parameters, no obvious influence of ferumoxytol on the direction or magnitude of changes in diastolic BP, RR, or temperature was observed in either dose group; however, slight decreases in mean systolic BP and mean pulse rate were observed at most time points.

Conclusions:

- Both dose regimens of ferumoxytol increased hemoglobin, hematocrit, and reticulocyte levels, which indicate that the iron was able to stimulate erythropoiesis.
- Both dose regimens of ferumoxytol transiently increased TSAT and serum iron levels, which indicates normal iron transport.
- Both dose regimens of ferumoxytol increased ferritin levels, which indicate the iron that was not immediately needed for erythropoiesis was transported to storage sites.

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µg/mL (Table 2). In addition, ferumoxytol was spiked into six different plasma samples at the LLOQ level and the recovery of ferumoxytol was 82% to 87% in each sample.

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4.3 Consult Review

4.4 Tabular listing of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Studies in Healthy Volunteers									
Phase I, PK and safety	7228-01 "A Phase I clinical investigation of Code 7228" Start date: 09-June-1999 Completion date: 04-August-1999	Module 5.3.3.1	To evaluate the PK and safety of ferumoxytol at increasing dose levels and at various rates of administration	Randomized, double-blind, placebo-controlled, single center, ascending dose	Ferumoxytol; 1 mg Fe/kg 2 mg Fe/kg 4 mg Fe/kg; IV	N=41 (randomized) Ferumoxytol-35; Placebo - 6	Healthy volunteers M: 22 F: 19	Single dose	Complete; Full report CSR 7228-01

CKD: Chronic kidney disease; HD: Hemodialysis; PK: Pharmacokinetics; IV: Intravenous; M: Male; F: Female; ESA: Erythropoiesis stimulating agent; PD: Peritoneal dialysis; CSR: Clinical study report.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase I Thorough QTc and PK	62,745-9 "A Phase I active and placebo-controlled study of the electrocardiogram effects and pharmacokinetics of ferumoxytol in healthy men and women" Start date: 22-May-2006 Completion date: 4-September-2006	Module 5.3.4.1	To define the effect of ferumoxytol on the QT interval; to assess PK and tolerability	Active- and placebo-controlled, randomized, double-blind (with respect to ferumoxytol and placebo), parallel group, single-center	Ferumoxytol: Two 510 mg doses of ferumoxytol administered on two consecutive days Placebo (saline): IV Moxifloxacin (400 mg) as active control: Oral	174 Total (randomized) Ferumoxytol - 58; Moxifloxacin - 58; Placebo-58	Healthy volunteers M: 102 F: 72	2 x 510 mg doses of ferumoxytol administered on two consecutive days	Complete; Full report CSR-62745-9

CKD: Chronic kidney disease; HD: Hemodialysis; PK: Pharmacokinetics; IV: Intravenous; M: Male; F: Female; ESA: Erythropoiesis stimulating agent; PD: Peritoneal dialysis; CSR: Clinical study report.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Studies in Patients with Chronic Kidney Disease									
Phase I PK and safety	62,745-2 "A Phase I open-label, rate administration, pharmacokinetic study of the safety of Code 7228 as an iron replacement therapy in chronic hemodialysis patients who are receiving supplemental EPO therapy"	Module 5.3.3.2	The objective of this study was to evaluate the safety and PK of two doses (125 and 250 mg) of ferumoxytol in subjects with CKD stage 5D who were on HD and receiving supplemental EPO therapy	Open-label, single center; Uncontrolled	Ferumoxytol; I - x 125 mg I - x 250 mg; IV	20: Total (enrolled) Ferumoxytol 125 mg - 10; Ferumoxytol 250 mg - 10	Patients with CKD stage 5D on hemodialysis M: 10 F: 10	Single dose	Complete; Full report CSR-62745-2
	Start date: 26-Sep-2001 Completion date: 10-Apr-2002								

CKD: Chronic kidney disease; HD: Hemodialysis; PK: Pharmacokinetics; IV: Intravenous; M: Male; F: Female; ESA: Erythropoiesis stimulating agent; PD: Peritoneal dialysis; CSR: Clinical study report.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen(s); Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase II, Safety/Efficacy	62,745-3 "A Phase II, Open-Label Study of the Safety and Efficacy of Two Parenteral Dose Regimens of Code 7228 (Compared With Oral Iron) as an Iron Replacement Therapy in Chronic Hemodialysis Patients Who Are Receiving Supplemental EPO Therapy"	Module 5.3.5.1	To evaluate the safety and efficacy of two parenteral dose regimens of ferumoxytol compared with oral iron	Multicenter, open label, Active control	Ferumoxytol: 8 x 128 mg 2 x 510 mg; IV Oral iron: 325 mg per day	36 Total (enrolled) Ferumoxytol 8 x 128 mg - 15; Ferumoxytol 2 x 510 mg - 11; Oral iron - 10	Patients with CKD stage 5D on hemodialysis M: 21 F: 15	8 x 128 mg doses of ferumoxytol within 4 weeks; 2x 510 mg of ferumoxytol within 2 weeks; daily oral iron for 8 sequential dialysis sessions (approx. 3 weeks)	Complete; Full report CSR-62745-3
	Start date: 20-Jan-2003 Completion date: 19-June-2003								

CKD: Chronic kidney disease; HD: Hemodialysis; PK: Pharmacokinetics; IV: Intravenous; M: Male; F: Female; ESA: Erythropoiesis stimulating agent; PD: Peritoneal dialysis; CSR: Clinical study report.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen(s); Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase II, Safety/Efficacy	62,745-4 "A Phase II, Open-Label Study of the Safety and Efficacy of Two Parenteral Dose Regimens of Ferumoxytol as an Iron Replacement Therapy in Chronic Kidney Disease Patients on Peritoneal Dialysis" Start date: 07-Oct-2002 Completion date: 27-Dec-2002	Module 5.3.5.2	To evaluate the safety and efficacy of two parenteral dose regimens of ferumoxytol in subjects with chronic renal failure (not on dialysis), or who were on PD	Multicenter, open label, Uncontrolled	Ferumoxytol; 4 x 255 mg 2 x 510 mg; IV	21 Total (enrolled) Ferumoxytol 4 x 255 mg - 10; Ferumoxytol 2 x 510 mg - 11	Patients with CKD stages 1-5 not on hemodialysis M: 9 F: 12	4 x 255 mg of ferumoxytol each separated by 2-3 days; 2 x 510 mg doses of ferumoxytol each separated by 2-3 days	Completed; Full report CSR-62745-4

CKD: Chronic kidney disease; HD: Hemodialysis; PK: Pharmacokinetics; IV: Intravenous; M: Male; F: Female; ESA: Erythropoiesis stimulating agent; PD: Peritoneal dialysis; CSR: Clinical study report.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase III, Safety/Efficacy	62,745-5 "A Phase III Study of the Safety and Efficacy of Ferumoxytol (Compared with Oral Iron) as an Iron Replacement Therapy in Hemodialysis Patients who are Receiving Supplemental Erythropoietin Therapy" Start date: 09-Aug-2004 Completion date: 24-Apr-2007	Module 5.3.5.1	To evaluate the safety and efficacy of ferumoxytol versus oral iron as an iron replacement therapy in subjects with CKD stage 5D on HD who were receiving supplemental ESA therapy	Randomized, multicenter, open label, Active control	Ferumoxytol: Post-amendment: 2 x 510 mg; Pre-amendment: 4 x 255 and 2 x 510 mg IV Oral iron: 200 mg per day	378 Total (randomized) Post-amendment: 230 Total; Ferumoxytol - 114; Oral Iron-116 Pre-amendment: 148 Total; Ferumoxytol 4x255 mg - 62; Ferumoxytol - 2x510 mg - 64; Oral Iron - 22	Patients with CKD stage 5D on hemodialysis Post-amendment: M: 130 F: 100 Pre-amendment: M: 63 F: 85	2 x 510 mg doses ferumoxytol within 7 days; 4 x 255 mg doses of ferumoxytol, within 14 days; or oral iron for 21 consecutive days	Complete; Full report CSR 62745-5

CKD: Chronic kidney disease; HD: Hemodialysis; PK: Pharmacokinetics; IV: Intravenous; M: Male; F: Female; ESA: Erythropoiesis stimulating agent; PD: Peritoneal dialysis; CSR: Clinical study report.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase III, Safety/Efficacy	62,745-6 "A Phase III Study of the Safety and Efficacy of Ferumoxytol (Compared with Oral Iron) as an Iron Replacement Therapy in chronic kidney disease patients not on dialysis" Start date: 10-May-2004 Completion date: 25-Sep-2006	Module 5.3.5.1	To evaluate the safety and efficacy of ferumoxytol versus oral iron for iron replacement therapy in subjects with CKD stages 1-5	Randomized, multicenter, open label, Active control	Ferumoxytol; 2 x 510 mg; IV; Oral iron: 200 mg per day	304 Total (randomized) Ferumoxytol - 228; Oral Iron - 76	Patients with CKD stages 1-5 M: 118 F: 186	2 x 510 mg doses of ferumoxytol within 5±3 days, or 21 consecutive days of oral iron	Complete; Full report CSR-62745-6

CKD: Chronic kidney disease; HD: Hemodialysis; PK: Pharmacokinetics; IV: Intravenous; M: Male; F: Female; ESA: Erythropoiesis stimulating agent; PD: Peritoneal dialysis; CSR: Clinical study report.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase III, Safety/Efficacy	62,745-7 "A Phase III Study of the Safety and Efficacy of Ferumoxytol (Compared with Oral Iron) as an Iron Replacement Therapy in chronic kidney disease patients not on dialysis" Start date: 02-June-2004 Completion date: 20-Dec-2006	Module 5.3.5.1	To evaluate the safety and efficacy of ferumoxytol versus oral iron for iron replacement therapy in subjects with CKD stages 1-5	Randomized, multicenter, open label; Active control	Ferumoxytol; 2 x 510 mg; IV Oral iron: 200 mg per day	304 Total (randomized) Ferumoxytol - 227; Oral Iron - 77	Patients with CKD stages 1-5 M: 125 F: 179	Two IV doses of ferumoxytol within 5±3 days, or 21 consecutive days of oral iron	Complete; Full report CSR-62745-7

CKD: Chronic kidney disease; HD: Hemodialysis; PK: Pharmacokinetics; IV: Intravenous; M: Male; F: Female; ESA: Erythropoiesis stimulating agent; PD: Peritoneal dialysis; CSR: Clinical study report.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase III, Safety	62,745-8 "A Double Blind, Placebo Controlled, Crossover Design, Multicenter Study of Intravenous Ferumoxytol Compared with Placebo" Start date: 27-Jan-2005 Completion date: 6-Sep-2006	Module 5.3.5.1	To compare the safety of a single 510 mg dose of IV ferumoxytol versus a single dose of IV saline placebo in subjects with all stages of CKD	Randomized, multicenter, double-blind, placebo controlled, crossover design	Ferumoxytol, 1 x 510 mg; IV Placebo (saline) IV	N=750 (randomized)	Patients with CKD stages 1-5 and 5D M: 347 F: 403	A single dose, followed by the crossover dose 7±2 days later	Complete; Full report CSR-62745-8

CKD: Chronic kidney disease; HD: Hemodialysis; PK: Pharmacokinetics; IV: Intravenous; M: Male; F: Female; ESA: Erythropoiesis stimulating agent; PD: Peritoneal dialysis; CSR: Clinical study report.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Studies in Medical Imaging Subjects (Patients and Healthy Volunteers)									
Phase I/IIa, Safety	58,254-2 "A Phase I/IIa Pilot Investigation Of Code 7228 As A Magnetic Resonance Angiography Contrast Agent" Start date: 01-Nov-2001 Completion date: 11-May-2002	Module 5.3.5.4	To evaluate the safety and imaging feasibility of ferumoxytol	Open label, single center, Uncontrolled	Ferumoxytol; ≤4 mg Fe/kg; IV	17 Total (enrolled) Healthy volunteers - 10; Imaging patients - 7	Healthy volunteers and imaging patients M: 12 F: 5	Single dose	Complete; Abbreviated report CSR-58254-2

CKD: Chronic kidney disease; HD: Hemodialysis; PK: Pharmacokinetics; IV: Intravenous; M: Male; F: Female; ESA: Erythropoiesis stimulating agent; PD: Peritoneal dialysis; CSR: Clinical study report.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase II, Safety	58,254-5 "A Phase 2 Investigation of Code 7228 as a Magnetic Resonance Angiography Contrast Agent" Start date: 7-Aug-2002 Completion date: 6-Sep-2005	Module 5.3.5.4	To evaluate the safety and imaging feasibility of ferumoxytol	Open label, single center; Uncontrolled	Ferumoxytol; ≤4 mg Fe/kg; IV	49 Total (enrolled) Healthy volunteers - 15; Imaging patients - 34	Healthy volunteers and imaging patients M: 29 F: 20	Single or incremental dose within the same imaging session	Complete; Abbreviated report CSR-58254-5

CKD: Chronic kidney disease; HD: Hemodialysis; PK: Pharmacokinetics; IV: Intravenous; M: Male; F: Female; ESA: Erythropoiesis stimulating agent; PD: Peritoneal dialysis; CSR: Clinical study report.

4.5 Cover sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology New Drug Application Filing and Review Form				
<u>General Information About the Submission</u>				
	Information		Information	
NDA Number	22-180	Brand Name	(Not Provided)	
OCP Division	DCP-5	Generic Name	Ferumoxytol	
Medical Division	DMIHP	Drug Class	Parenteral Iron preparation	
OCPB Reviewer	Young Moon Choi	Indication(s)	for the treatment of iron deficiency anemia in patients with chronic kidney disease (CKD)	
OCPB Team Leader	Brian Booth	Dosage Form	30 mg elemental iron/ml for intravenous injection and provided in single use vials in three sizes: (1) 510 mg iron in 17 ml filled in vial size of <input checked="" type="checkbox"/> ml (2) 255 mg of iron in 8.5 ml filled vial size of <input checked="" type="checkbox"/> ml (3) 127.5 mg of iron in 4.25 ml filled in <input checked="" type="checkbox"/> ml vial size	
		Dosing Regimen	Doses up to 510 mg of ferumoxytol can be given as a rapid IV injection at a rate of up to 1 ml/sec (30 mg/sec). A second dose up to 510 mg may be administered as soon as <input checked="" type="checkbox"/> days following the first dose. Patients may continue to require therapy with intravenous iron to maintain target levels of hemoglobin and laboratory parameters of iron storage within acceptable limits.	
Date of Submission	12/18/07	Route of Administration	Intravenous administration	
Estimated Due Date of OCPB Review	8/19/08	Sponsor	AMAG pharmaceuticals, Inc.	
PDUFA Due Date	10/19/08	Priority Classification	S (Not NME)	
Division Due Date	9/19/08			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				

b(4)

Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	x	1		
multiple dose:				
Patients-				
single dose:	x	1		Pop PK analysis
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	x			From Healthy study and Patients study
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				Analysis from PK studies
pediatrics:				Waiver /Deferral request
geriatrics:				
renal impairment:				Target patients are CKD patients; From hemodialysis patients
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PPD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	x			POP PK and modeling Analysis were adopted for PK in patients Data looks rich but seems not appropriate (only up to 3 hours); Need to send consult to PM team.
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Thorough QT study	x	1		
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		3		

Filability and QBR comments		
	"X" if yes	Comments
Application filable	x	
Comments sent to firm		<p>Following comment needs to be sent to the firm:</p> <p>It is noted that the PK-PD correlation (i.e., plasma concentration or dose vs. safety or efficacy parameters) have not been reported in clinical pharmacology section. Please provide any available data about exposure vs. safety and/or efficacy parameters such as Hgb, serum ferritin, and TSAT.</p>
QBR questions (key issues to be considered)		<p>Validation of new analytical method (i.e., magnetic resonance spectrometric technique)</p> <p>PK analysis of ferumoxytol in patients (POP PK and modeling: Data rich but seems not appropriate to evaluate PK parameters): Need to consult to PMetric team.</p> <p>Thorough QTc study needs to be consulted to IRT.</p>
Other comments or information not included above		<p>Dose justification (exposure-response evaluation):</p> <p>In two phase 2 studies, the sponsor evaluated two dosage regimen with efficacy parameters such as Hgb, serum ferritin, and TSAT as measures of underlying iron deficiency anemia. These data will be focused during the review. Furthermore, other available data about exposure-response relation will be requested (Refer to the above comment.)</p>
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Young-Moon Choi
10/8/2008 04:54:44 PM
BIOPHARMACEUTICS

Brian Booth
10/9/2008 08:38:38 AM
BIOPHARMACEUTICS

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-180	Brand Name	(Not Provided)
OCP Division	DCP-5	Generic Name	Ferumoxytol
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Date of Submission	12/18/07	Route of Administration	Intravenous administration
Estimated Due Date of OCPB Review	8/19/08	Sponsor	AMAG pharmaceuticals, Inc.
PDUFA Due Date	10/19/08	Priority Classification	S (Not NME)
Division Due Date	9/19/08		

b(4)

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
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Blood/plasma ratio:				
Plasma protein binding:				

Pharmacokinetics (e.g., Phase I) -				
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multiple dose:				
Patients-				
single dose:	x	1		Pop PK analysis
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	x			From Healthy study and Patients study
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				Analysis from PK studies
pediatrics:				Waiver /Deferral request
geriatrics:				
renal impairment:				Target patients are CKD patients; From hemodialysis patients
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
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traditional design; single / multi dose:				
replicate design; single / multi dose:				
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Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Thorough QT study	x	1		
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				

Literature References			
Total Number of Studies		3	
Filability and QBR comments			
	"X" if yes	Comments	
Application filable ?	x		
Comments sent to firm ?		<p>Following comment needs to be sent to the firm: It is noted that the PK-PD correlation (i.e., plasma concentration or dose vs. safety or efficacy parameters) have not been reported in clinical pharmacology section. Please provide any available data about exposure vs. safety and/or efficacy parameters such as Hgb, serum ferritin, and TSAT.</p>	
QBR questions (key issues to be considered)		<ul style="list-style-type: none"> ▪ Validation of new analytical method (i.e., magnetic resonance spectrometric technique) ▪ PK analysis of ferumoxytol in patients (POP PK and modeling: Data rich but seems not appropriate to evaluate PK parameters): Need to consult to PMetric team. ▪ Thorough QTc study needs to be consulted to IRT. 	
Other comments or information not included above		<p>Dose justification (exposure-response evaluation): In two phase 2 studies, the sponsor evaluated two dosage regimen with efficacy parameters such as Hgb, serum ferritin, and TSAT as measures of underlying iron deficiency anemia. These data will be focused during the review. Furthermore, other available data about exposure-response relation will be requested (Refer to the above comment.)</p>	
Primary reviewer Signature and Date			
Secondary reviewer Signature and Date			

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Young-Moon Choi
2/19/2008 11:11:33 AM
BIOPHARMACEUTICS